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(54) Title: ANTI-VIRAL COMPOUNDS THAT BIND THE ACTIVE SITE OF INFLUENZA NEURAMIDASE AND DISPLAY *IN VIVO* ACTIVITY AGAINST ORTHOMYXOVIRUS AND PARAMYXOVIRUS

(57) Abstract

A pharmacologically active composition of the invention comprises (i) a virus-inhibiting amount of a compound that binds the active site of influenza virus neuraminidase and that displays *in vivo* activity against orthomyxovirus or paramyxovirus; and (ii) a pharmaceutically-acceptable carrier for the compound which is preferably suitable for intranasal administration. In preferred embodiments, the compound possesses a K_i value, with respect to the active site, of less than 10^{-7} M. Preferably, the compound is a carbocyclic or heterocyclic compound comprised of a 5-, 6- or 7-membered ring carrying a substituent selected from a carboxylate moiety and an analogue thereof, the ring and the substituent being positioned in the same plane.

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Anti-viral compounds that bind the active site of influenza neuramidase and display in-vivo activity against orthomyxovirus paramyxovirus

Background of the Invention

The present invention relates to a new class of anti-viral compounds, exemplified by certain 2-deoxy and 2,3-dehydro analogues of α-D-neuraminic acid, and to their use, via inhibition of viral neuraminidases, for the prophylaxis and for the treatment of infections such as influenza, Newcastle disease and fowl plague.

Enzymes with the ability to cleave N-acetyl neuraminic acid (NANA), also known as sialic acid, from other sugars are present in many microorganisms. These include bacteria such as Vibrio cholerae, Clostridium perfringens, Streptococcus pneumoniae, and Arthrobacter sialophilus, and viruses such as influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus, and Sendai virus. Most of these viruses are of the orthomyxovirus or paramyxovirus groups, and carry a neuraminidase activity on the surface of the virus particles.

Many of the neuraminidase-possessing organisms are major pathogens of man and/or animals, and some, such as influenza virus, Newcastle disease virus, and fowl plague virus, cause diseases of enormous economic importance.

It has long been thought that inhibitors of neuraminidase activity might prevent infection by neuraminidase-bearing viruses. But while several such inhibitors are known, none has been shown to possess antiviral activity in vivo. Most of the known neuraminidase inhibitors are analogues of neuraminic acid, such as 2-deoxy-2,3-dehydro-N-acetylneuraminic acid (DANA) and its derivatives. See, e.g., Meindl et al., Virology 1974 58 457-63. The most active of these is 2-deoxy-2,3-dehydro-N-trifluoracetyl-neuraminic acid (FANA), which inhibits multi-cycle replication of influenza and parainfluenza viruses in vitro. See Palese et al., Virology 1974 59 490-498.

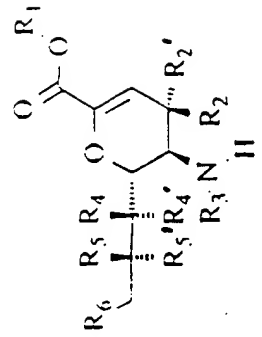
Table 1 below presents a listing of known N-acetylneuraminic acid derivatives. Many of these compounds are active against neuraminidase from V. cholerae or Newcastle disease virus as well as that from influenza virus. Neuraminidase in at least some strains of influenza or parainfluenza viruses is also inhibited by 3-aza-2,3,4-trideoxy-4-oxo-D-arabinoctonic acid δ-lactone and O-α-N-acetyl-D-neuraminosyl-(2--->3)-2-acetamido-2-deoxy-D-glucose Zakstel'skaya et al., Vop. Virol. 1972 17 223-28.

Neuraminidase from Arthrobacter sialophilus is inhibited by the glycals 2,3-dehydro-4-epi-N-acetyl-neuraminic acid, 2,3-dehydro-2-deoxy-N-acetylneuraminic acid and 5-acetamido-2,6-anhydro-2,3,5-trideoxy-D-manno-non-2-en-4-ulosonate, and by their methyl esters. See Kumar et al., Carbohydrate Res. 1981 94 123-130; Carbohydrate Res. 1982 103 281-285.

The thio analogues 2-α-azido-6-thio-neuraminic acid and 2,3-dehydro-6-thioneuraminic acid, Mack & Brossmer, Tetrahedron Letters 1987 28 191-194, and the fluorinated analogue N-acetyl-2,3-difluoro-α-D-neuraminic acid, Nakajima et al., Agric. Biol. Chem. 1988 52 1209-1215, were reported to inhibit neuraminidase, although the type of neuraminidase was not identified. Schmid et al., Tetrahedron Letters 1988 29 3643-3646, described the synthesis of 2-deoxy-N-acetyl-α-D-neuraminic acid, but did not report its activity or otherwise against neuraminidase.

TABLE 1

Known 2,3-dehydro derivatives on N-acetylneuraminic acid



	R_1	R_2	R_2'	R_3	R_4	R_4'	R_5	R_5'	R_6
1	H	H	OH	CH_3CO-	H	OH	OH	H	OH
2	H	H	OH	NH_2CO-	H	OH	OH	H	OH
3	H	H	OH	HCO-	H	OH	OH	H	OH
4	H	H	OH	FCH_2CO-	H	OH	OH	H	OH
5	H	H	OH	F_2CHCO-	H	OH	OH	H	OH
6	H	H	OH	F_3CCO-	H	OH	OH	H	OH
7	H	H	OH	$ClCH_2CO$-	H	OH	OH	H	OH
8	H	H	OH	ICH_2CO-	H	OH	OH	H	OH
9	H	H	OH	$CNCH_2CO$-	H	OH	OH	H	OH
10	H	H	OH	NH_2CH_2CO-	H	OH	OH	H	OH
11	H	H	OH	$HSCH_2CO$-	H	OH	OH	H	OH
12	H	H	OH	$CH_2CONHCH_2CO$-	H	OH	OH	H	OH
13	H	H	OH	$(CH_3)_2NCH_2CO$-	H	OH	OH	H	OH

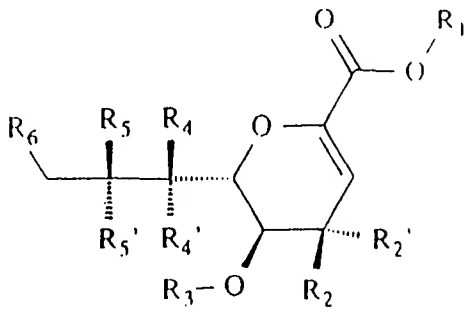
TABLE 1 (cont.)

14	H	H	OH	$NH_2CH_2CH_2CO$-	H	OH	OH	H	OH
15	H	H	OH	$CH_3CONHCH_2CHCO$-	H	OH	OH	H	OH
16	H	H	OH	$HOOCCH_2CH_2CO$-	H	OH	OH	H	OH
17	H	H	OH	HOOCCH=CHCO-	H	OH	OH	H	OH
18	H	H	OH	Neu5Acyl2enNHCOCH_2SCH_2CO-	H	OH	OH	H	OH
19	H	H	OH	$HOCH_2CO$-	H	OH	OH	H	OH
20	H	H	OH	CH_3CH_2CO-	H	OH	OH	H	OH
21	H	H	OH	$CH_3CH_2CH_2CO$-	H	OH	OH	H	OH
22	H	H	OH	C_6H_5CO-	H	OH	OH	H	OH
23	H	H	OH	$C_6H_5CH_2CO$-	H	OH	OH	H	OH
24	CH_3	H	OH	CH_3CO-	H	OH	OH	H	OH
25	CH_3	OH	H	CH_3CO-	H	OH	OH	H	OH
26	CH_3	H	OH	CH_3CO-	H	OH	OH	H	OTr
27	CH_3	OH	H	CH_3CO-	H	OH	OH	H	O(p-$CH_3OC_6H_4$)
28	CH_3	H	OH	CH_3CO-	H	OH	OH	H	O(p-$CH_3OC_6H_4$)
29	CH_3	=O		CH_3CO-	H	OH	OH	H	O(p-$CH_3OC_6H_4$)
30	CH_3	=O		CH_3CO-	H	OH	OH	H	OTr
31	CH_3	=O		CH_3CO-	H	OH	OH	H	OH
32	H	=O		CH_3CO-	H	OH	OH	H	OH

TABLE 1 (cont.)

	R_1	R_2	R_2'	R_3	R_4	R_4'	R_5	R_5'	R_6
33	H	H	OH	CH_3CO-	H	H	OH	H	OH
34	H	H	OH	CH_3CO-	H	OH	H	H	OH
35	H	H	OH	CH_3CO-	H	OH	OH	H	H
36	H	H	H	CH_3CO-	H	H	OH	H	OH
37	CH_3	H	CH_3COO-	CH_3CO-	H	H	CH_3COO-	H	CH_3COO-
38	CH_3	H	CH_3COO-	CH_3CO-	H	CH_3COO-	H	H	CH_3COO-
39	CH_3	H	CH_3COO-	CH_3CO-	H	CH_3COO-	CH_3COO-	H	H
40	CH_3	H	H	CH_3CO-	H	H	CH_3COO-	H	CH_3COO-
41	CH_3	H	$C_6H_5CH_2O$-	CH_3CO-	H	$C_6H_5CH_2O$-	$C_6H_5CH_2O$-	H	$C_6H_5CH_2O$-
42	CH_3	H	CH_3COO-	CH_3CO-	H	CH_3COO-	CH_3COO-	H	CH_3COO-
43	CH_3	H	CH_3COO-	CH_3CO	H	CH_3COO-	H	H	CH_3COO-
44	CH_3	H	CH_3COO-	CH_3CO	H	CH_3COO-	H	CH_3COO-	H
45	CH_3	H	CH_3COO-	CH_3CO	H	CH_3COO-	H	CH_3COO-	2αNeu5Ac

TABLE 1 (cont.)



	R_1	R_2	R_2'	R_3	R_4	R_4'	R_5	R_5'	R_6
46	$C_6H_5CH_2$	H	CH_3COO-	CH_3CO	H	CH_3COO-	CH_3COO-	H	CH_3COO-

Compounds 1-18 P.Meindl, G. Bodo, P. Palese, J. Schulman and H. Tuppy. Inhibition of Neuraminidase Activity by Derivatives of 2-Deoxy-2,3,-dehydro-N-acetylneuraminic Acid. *Virology* 58, 457-463(1974).

Compounds 19-23 P.Meindl and H. Tuppy. Ueber 2-Desoxy-2,3-deshydro-sialinsaeuren I. Mitt. : Synthese und Eigenschaften von 2-Desoxy-2,3-deshydro-N-acylneuraminsaeuren und deren Methylestern. *Mh. Chem.* 100 (4) 1295-1306 (1969)

Compounds 24-32 M. Flashner et al. Methyl-5-acetamido-2,6-anhydro-3,5 -dideoxy-D-*manno*-non-2-en-4-ulosonate. *Carbohydrate Research* 103, 281-285(1982)

TABLE 1 (cont.)

Compounds 33-40	E. Zbiral et al. Synthesis of 2,7-, 2,8-, and 2,9-Dideoxy and 2,4,7-Trideoxy-2,3-didehydro-*N*-acetylneuraminic Acids and Their Behavior Towards Sialidase from *Vibrio cholerae* *Liebigs Ann. Chem* **1989**, 159 165.
Compounds 41-42	T. Ogawa and Y. Ito. An Efficient Approach to Stereoselective Glycosylation of N-Acetylneuraminic Acid: Use of Phenylselenyl Group as a Stereocontrolling Auxillary. *Tetrahedron Letters* 28, (49), 6221-6224(1987).
Compounds 43-45	T. Goto et al. Synthesis of (α2-9) and (α2-8) Linked Neuraminylneuraminic Acid Derivatives. *Tetrahedron Letters* 27, (43), 5229-5232(1986).
Compound 46	H. Ogura et al. Studies on Sialic Acids XV. Synthesis of α and β-O- Glycosides of 3-Deoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonic Acid (KDN). *Chem. Pharm. Bull.* 36, (12), 4807-4813(1988)

Meindl and Tuppy, Hoppe-Seyler's Z. Physiol. Chem. 1969 350 1088, described hydrogenation of the olefinic double bond of 2-deoxy-2,3-dehydro-N-acetylneuraminic acid to produce the ß-anomer of 2-deoxy-N-acetylneuraminic acid. This ß-anomer did not inhibit Vibrio cholerae neuraminidase.

The most potent in vitro inhibitors of viral neuraminidase have thus been identified as compounds that are based on the neuraminic acid framework, and these are thought by some to be transition-state analogues. Miller et al., Biochem. Biophys. Res. Comm. 1978 83 1479. But while many of the aforementioned neuraminic acid analogues are competitive inhibitors of neuraminidases, none is known to have anti-viral activity in vivo. For example, although a half-planar, unsaturated 6-member ring system has been asserted to be important for inhibitory activity, see Dernick et al. in ANTIVIRAL CHEMOTHERAPY (K.K. Gauri ed.) Academic Press, 1981, at pages 327-336, some compounds characterized by such a system, notably FANA, have been reported not to possess in vivo anti-viral activity. See Palese and Schulman in CHEMOPROPHYLAXIS AND VIRUS INFECTION OF THE UPPER RESPIRATORY TRACT, Vol. 1 (J.S. Oxford ed.) CRC Press, 1977, at pages 189-205. Accordingly, the conventional wisdom has been that compounds exhibiting in vitro inhibition of viral neuraminidase would not effect an in vivo blockade of virus infection.

Summary of the Invention

It is therefore an object of the present invention to provide improved inhibitors of neuraminidase which have anti-viral activity in vivo.

It is also an object of the present invention to provide medicinal compositions which can be used to prevent or ameliorate symptoms of viral infection.

It is a further object of the present invention to provide means for producing such medicinal compositions.

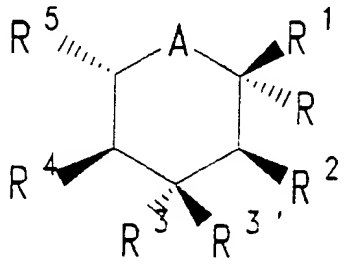
In achieving this object there has been provided, in accordance with one aspect of the invention, a biologically active substance that binds the active site

("receptor") of influenza virus neuraminidase such that said substance displays anti-orthomyxovirus or paramyxovirus activity in an animal. In a preferred embodiment, the active substance displays (a) in vitro activity in an assay which measures binding of the active site of influenza virus neuraminidase; and (b) in vivo anti-orthomyxovirus or paramyxovirus activity. Preferably, the in vivo activity is displayed in mice or ferrets challenged intranasally with influenza virus.

According to another aspect, the present invention provides a biologically active substance which possesses stereochemical complementarity to an enzyme active site comprised of amino acids positioned at atomic coordinates enumerated as part of Figure 1 below, or a subset thereof, and said substance displays in vivo activity against an orthomyxovirus or a paramyxovirus. Preferably, the stereochemical complementarity is such that the compound has a K_i for said active site of less than 10^{-7}M. More preferably, the K_i value is less than 0.5×10^{-8}M.

It is also preferred, according to either aspect of the present invention, that the substance be a carbohydrate comprising a non-mutarotatable anomeric carbon atom. More preferably, this carbon atom is optionally substituted by a functional group. Even more preferably, the functional group is carried on the C_2 carbon.

In one preferred embodiment the compound is a novel 2-deoxy derivative of α-D-neuraminic acid of general structural formula I:



I

and pharmacologically acceptable salts or derivatives thereof, wherein

A denotes O,

R denotes hydrogen, CN, CH-NHR^6, CH_2OR^6, CH_2F, CH_3, $Sn(R^6)_3$, $Si(R^6)_3$ or SR^7, where R^7 is an alkyl group which has an alkyl chain of 1 to 6 carbons; or an aryl group wherein the aryl moiety is mono-, di- or tri-substituted with halogen, amino, hydroxyl or carboxyl,

R^1 denotes COOH, $P(O)(OH)_2$, NO_2, SOOH, SO_3H, tetrazole, CH_2CHO, CHO, $CH(CHO)_2$ or, where R^1 is COOH, $P(O)(OH)_2$, SOOH or SO_3H, an ethyl, methyl or pivaloyl ester thereof,

R^2 denotes H, OR^6, F, Cl, Br, CN, NHR^6, SR^6 or CH_2X, wherein X is NHR^6, halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; or an unsubstituted aryl group or an aryl substituted by a halogen, an allyl group, an OH group, an NO_2 group, an NH_2 group or a COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, $N(R^6)_2$, SR^6 or OR^6,

R^4 denotes $NHC(=O)-R^7$, where R^7 is an unsubstituted or halogen-substituted linear or cyclic alkyl group of 1 to 6 carbon atoms, or SR^6, OR^6, COOH or alkyl/aryl ester thereof, NO_2, $C(R^6)_3$, CH_2COOH or alkyl/aryl ester thereof, CH_2NO_2 or CH_2NHR^7, and

R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$ where Y is O, S or H, and successive Y moieties in an R^5 group are the same or different, subject to the provisos that

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, then said compound cannot have both

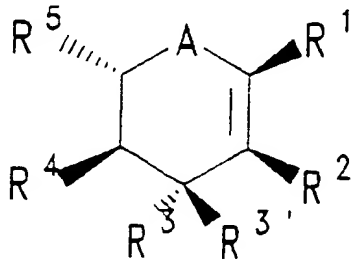
(a) an R^2 that is hydrogen and

(b) an R^4 that is NH-acyl,

(ii) R^7 is not CH_3, CH_2CH_3, phenyl, glucosyl, galactosyl, mannosyl, acetyl, benzoyl, cyclohexyl or substituted cyclohexyl and

(iii) R^6 represents a covalent bond when Y is hydrogen. The compound is preferably one selected from the group consisting of methyl N-acetyl-4,7,8,9-tetra-O-acetyl-2-deoxy-2α-allylthioneuraminate, and sodium N-acetyl-2-deoxy-2α-allylthioneuraminate.

In a second preferred embodiment, the compound has general formula II:



II

where A is oxygen and where R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and R^6 are as defined in general formula I above, subject to the provisos that, in general formula II,

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, then said compound cannot have both

(a) an R^2 that is hydrogen and

(b) an R^4 that is NH-acyl, and

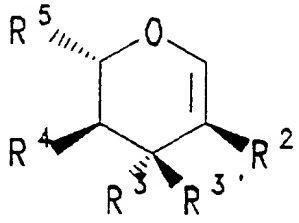
(ii) R^6 represents a covalent bond when Y is hydrogen, and pharmaceutically acceptable salts or derivatives thereof. Preferably, the compound is synthesized using an intermediate selected from the group consisting of 3,4,6-tri-O-acetyl-2-deoxy-β-L-arabinohexapyranosyl thiophenoxide; 4-O-benzyl-3,6-bis (t-butylmethylsilyloxy)-2-deoxy-β-L-arabino-hexapyranosyl thiophenoxide; 4-O-benzyl-3,6-bis(t-butylmethylsilyloxy)-2-deoxy-β-L-arabinohexa-pyranosyl phenylsulphone; α-carboxymethyl-β-phenysulphonyl-4-O-benzyl-3,6-bis(t-butyldimethylsilyloxy)-2-deoxy-L-arabinohexapyranose; methyl-4-O-benzyl-3,6-bis(t-butyldimethylsilyloxy)-2-deoxy-α-L-arabinohexapyranosyl-carboxylate and methyl-N-acetyl-4,7,8,9-tetra-O-acetyl-2β-chloro-2-deoxy-D-neuraminate.

According to a third aspect of the invention there is provided a method of synthesis of a compound according to general formula I, comprising the steps of providing an alkyl

N-acetyl neuraminate, reacting said alkyl N-acetyl neuraminate with an alcohol in the presence of an acid catalyst to yield the corresponding ester, acylating and halogenating the ester by reaction with an acyl halide, treating the halogenated and acylated ester with a nucleophile to effect halogen-nucleophile exchange, deacylating and deesterifying the resulting compound under hydrolytic conditions, and recovering the compound of general formula I.

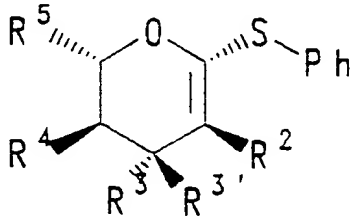
In an alternative embodiment of this aspect of the present invention, there is provided a method of synthesis of a desired compound of general formula I which comprises the steps of:

(a) treating a glycal of formula (i)



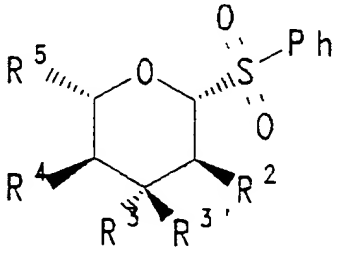
(i)

with hydrogen chloride and then with sodium thiophenoxide to form a thioglycoside of formula (ii) below



(i i)

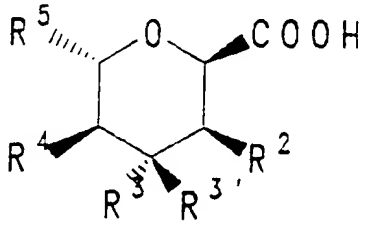
(b) oxidizing the thioglycoside with metachloroperoxybenzoic acid to form a sulphone of formula (iii)



(i i i)

and either

(c) reacting the sulphone with lithium diisopropyl amide and then with dimethylcarbonate to form alpha and beta C-1 substituted sugars of formula (iv)



(iv)

and

(c') isolating the C-1 substituted sugar,

or

(d) reacting the sulphone with lithium diisopropyl amide in the presence of lithium naphthalenide and a compound containing a COOH, $P(O)(OH)_2$, or SOOH group and

(d') isolating the desired compound of formula I.

In step (d) the compound containing the $P(O)(OH)_2$ group is preferably diethyl chlorophosphate. Other compounds of the present invention can be synthesized using the products of step (c') or step (d') as starting materials, as will be readily appreciated by those skilled in the art.

According to a fourth aspect, the invention provides a pharmacologically active composition comprising (i) an orthomyxovirus or paramyxovirus-inhibiting amount of a substance that binds the active site of influenza virus neuraminidase such that said substance displays anti-orthomyxovirus or paramyxovirus activity in an animal and (ii) a physiologically-compatible carrier diluent or excipient for said substance. The substance is preferably a compound that conforms to general formula I or II except for the fact that the exclusionary provisos set out above do not apply.

According to a fifth aspect, the invention provides a method of preventing or ameliorating the symptoms of an orthomyxovirus or paramyxovirus infection, comprising the step of administering to an animal a virus-inhibiting amount of a substance that binds the active site of influenza virus

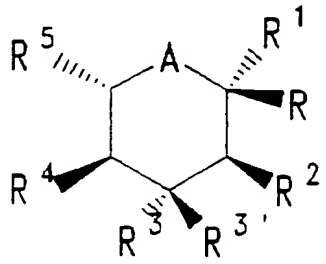
neuraminidase such that the substance displays anti-orthomyxovirus or paramyxovirus activity in an animal. The substance may be administered orally, intranasally, buccally or sublingually.

In each of these five aspects of the invention, the virus is preferably selected from the group consisting of influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus, and Sendai virus. In the method according to the fourth aspect of the invention, it is particularly preferable that the virus either

(A) is selected from the group consisting of influenza virus, parainfluenza virus, Sendai virus and mumps virus, and the animal is a human, or

(B) is Newcastle disease virus or fowl plague virus, and the animal is a bird.

According to a sixth aspect, the invention provides novel glycosyl halides of general formula III, which are useful as intermediates in the synthesis of compounds of general formula I above:



III

wherein

R may be F, Cl or Br when R^2 is not H, F, Cl or Br;

if R^3, $R^{3'}$ is OR^6 or H then R^4 is NH-Acyl; and

A, R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and R^6 are as defined in general formula I above. Formula III compounds can be used as glycosyl donor intermediates in the synthesis of compounds of general formula I.

According to a seventh aspect of the invention, there is provided an improved method of synthesis of glycosyl halides of general formula III comprising the step of

treating the corresponding neuraminic acid analogue with excess acetyl halide at room temperature under a nitrogen atmosphere until no starting material is observable by thin layer chromatography, and recovering the desired glycosyl halide compound.

Brief Description of the Drawings

Figure 1 depicts an exemplary influenza-viral neuraminidase, that of A/Tokyo/3/67, in terms of refined atomic coordinates in Angstrom units (accuracy: ± 0.3 Å) for all amino-acid moieties, including the active site, of the enzyme molecule. The coordinates are in relation to a Cartesian system of orthogonal axes.

Figure 2 is a detailed representation, provided in terms of refined atomic coordinates as in Figure 1, of N-acetyl neuraminic acid as observed bound to influenza virus neuraminidase as described in Figure 1.

Figure 3 shows the atomic coordinates in Angstrom units of 3-fluoro-1,1,1,3,5,5,5-heptanitropentane in its predicted mode of binding to the active site of the influenza viral neuraminidase of Figure 1.

Figures 4 and 6 are schematic representations of a general scheme for the synthesis, respectively, of two subclasses of anti-viral agents within the present invention. Each of Figures 5 and 7 represents schematically a particular synthesis according to Figures 4 and 6, respectively.

Detailed Description of Preferred Embodiments

A refined view of the three-dimensional structure of the active site of influenza virus neuraminidase has now been developed (with errors of the order of 0.3 Å) that enables the production of molecules which tightly bind the enzyme active site, something that heretofore could not have been accomplished based, for example, on extant information regarding the crystal structure of N2 influenza virus neuraminidase soaked with neuraminic acid. See Varghese et al., Nature 1983 303 35-40. Notwithstanding expectations to the contrary regarding the import of neuraminidase-binding

capability, it has also been discovered that compounds possessing high affinity for the enzyme active site are also prime candidates for in vivo anti-viral agents, which property is routinely ascertainable by means of a conventional animal assay, as described in greater detail below.

The mechanism or mechanisms underlying this beneficial correlation between neuraminidase affinity and in vivo anti-viral activity are not fully clarified. But the tight binding of the active site, preferably with an affinity on the order of 10^{-8} M, is understood to arise from an enhanced stereochemical complementarity, relative to known in vitro-effective neuraminidase inhibitors, between compounds of the present invention and the active site, which favors desolvation of the compound. Such enhanced complementarity is accomplished, in accordance with the present invention, by assuring that the structure of the receptor-binding molecule correlates, in the manner of the classic "lock-and-key" visualization of ligand-receptor interaction, with the critical features of the active site.

A molecule within the present invention can be designed, based on the atomic-coordinate information set out in Figure 1, so that selected portions of the molecule match surface residues positioned within the substrate binding site on the neuraminidase molecule. By "match" it is meant that the identified portions interact with the surface residues, for example, via hydrogen-bonding and by enthalpy-reducing Van der Waals interactions which promote desolvation of the molecule within the site, in such a way that retention of the molecule in the site is favored energetically.

Such stereochemical complementarity, pursuant to the present invention, is characteristic of a molecule that matches intra-site surface residues located in the vicinity of coordinate point (92, 92, 67 Å) in Figure 1. The latter point is near tyrosine 406 of the neuraminidase molecule, and defines the site where sialic acid has been observed to bind. Tyrosine 406 is surrounded by residues including amino acids 118, 119, 151, 224, 276, 277, 292 and 371, that define a

depression on the surface of the enzyme molecule and that do not vary from strain to strain, as illustrated by the sequence alignments for neuraminidases from different strains of influenza virus. See Colman & Ward, Curr. Topics Microbiol. Immunol., 1985 114 177.

This surface depression represents the neuraminidase active site which is highly conserved. According to the present invention, therefore, the effort of matching portions of an anti-viral agent within the present invention should be directed to the invariant residues which define the active site. Chemical entities which are complementary to the shape of an enzyme active site characterized by the aforementioned invariant structural elements are able to bind to the active site and, when the affinity of binding is sufficiently strong -- as reflected by a K_i preferably on the order of 10^{-7} or less -- will prohibit access of natural substrate to the site.

By way of illustration, for the compound 2-deoxy-N-acetyl-α-D-neuraminic acid (see Examples 1, 4, 18, 24 and 25), a carboxylate substituent on carbon C_2 interacts with the guanidinium moiety of arginine 371 in the neuraminidase active site, while the glycerol side chain makes (i) Van der Waals contacts with the hydrocarbon moiety of arginine 224 and (ii) hydrogen bonds with the carboxylate of glutamic acid 276. By the same token, the carboxylate substituent and glycerol side chain, respectively, of each of the compounds N-acetyl-neuraminic acid, 2,3-dehydro-N-acetyl-neuraminic acid and 2,3-dehydro-N-trifluroacetyl-D-neuraminic acid interact in similar fashion with the same residues of the active site.

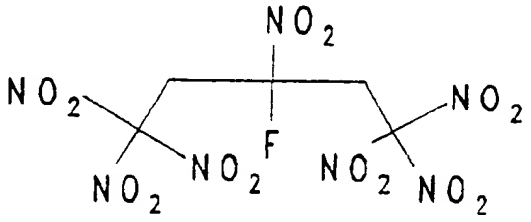
In general, the design of a molecule possessing stereochemical complementarity can be accomplished by means of techniques that optimize, either chemically or geometrically, the "fit" between a molecule and a target receptor. Known techniques of this sort are reviewed by Sheridan and Venkataraghavan, Acc. Chem Res. 1987 20 322; Goodford, J. Med. Chem. 1984 27 557; Beddell, Chem. Soc. Reviews 1985, 279; and Hol, Angew. Chem. 1986 25 767, the

respective contents of which are hereby incorporated by reference. See also Blundell et al., Nature 1987 326 347 (drug development based on information regarding receptor structure).

Thus, there are two preferred approaches to designing a molecule, according to the present invention, that complements the active site of influenza virus neuraminidase. By the geometric approach, the number of internal degrees of freedom (and the corresponding local minima in the molecular conformation space) is reduced by considering only the geometric (hard-sphere) interactions of two rigid bodies, where one body (the active site) contains "pockets" or "grooves" that form binding sites for the second body (the complementing molecule, as ligand). The second preferred approach entails an assessment of the interaction of respective chemical groups ("probes") with the active site at sample positions within and around the site, resulting in an array of energy values from which three-dimensional contour surfaces at selected energy levels can be generated.

The geometric approach is illustrated by Kuntz et al., J. Mol. Biol. 1982 161 269, the contents of which are hereby incorporated by reference, whose algorithm for ligand design is implemented in a commercial software package distributed by the Regents of the University of California and further described in a document, provided by the distributor, which is entitled "Overview of the DOCK Package, Version 1.0,", the contents of which are hereby incorporated by reference. Pursuant to the Kuntz algorithm, the shape of the cavity represented by the neuraminidase active site is defined as a series of overlapping spheres of different radii. One or more extant data bases of crystallographic data, such as the Cambridge Structural Database System maintained by Cambridge University (University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.) and the Protein Data Bank maintained by Brookhaven National Laboratory (Chemistry Dept. Upton, NY 11973, U.S.A.), is then searched for molecules which approximate the shape thus defined.

Molecules identified in this way, on the basis of geometric parameters, can then be modified to satisfy criteria associated with chemical complementarity, such as hydrogen bonding, ionic interactions and Van der Waals interactions. For example, the compound 3-fluoro-1,1,1,3,5,5,5-heptanitropentane (FHNP) is represented by the structural formula



and has been identified, pursuant to the Kuntz algorithm, as a molecule that complements, as represented according to the aforementioned geometric definition. Based on the orientation predicted using the above-mentioned software package, modifications in the FHNP molecule would be made in order to adjust localized hydrophilicity or hydrophobicity and, thereby, improve the degree of stereochemical complementarity. For example, from the predicted orientation shown in Figure 3 it is apparent that replacement of the nitro group N13, 026, 027 by a methylene amino group could improve the hydrogen bonding complementarity to glutamic acid 277 on the neuraminidase.

The chemical-probe approach to ligand design is described, for example, by Goodford, J. Med. Chem. 1985 28 849, the contents of which are hereby incorporated by reference, and is implemented in several commercial software packages, such as GRID (product of Molecular Discovery Ltd., West Way House, Elms Parade, Oxford OX2 9LL, U.K.). Pursuant to this approach, the chemical prerequisites for a site-complementing molecule are identified at the outset, by probing the active site (as represented via the atomic coordinates shown in Fig. 1) with different chemical probes, e.g., water, a methyl group, an amine nitrogen, a carboxyl oxygen, and a hydroxyl. Favored sites for interaction between the active site and each probe are thus determined,

and from the resulting three-dimensional pattern of such sites a putative complementary molecule can be generated.

The chemical-probe approach is especially useful in defining variants of a molecule known to bind the target receptor. Since sialic acid is such a molecule, vis-a-vis the neuraminidase active site, crystallographic analysis of sialic acid bound to neuraminidase provides useful information regarding the interaction between an archetype ligand and the active site of interest. In particular, it has been found that sialic acid binds to neuraminidase in a distorted conformation, with the carboxylate group pushed into the plane of the sugar (see Figure 2).

Since this carboxylate-planar feature is inherent in the DANA molecule and molecules that are "DANA-like" by virtue of having an sp^2-hybridized system at C_2/C_3, no distortion is needed for such molecules to fit -- that is, to possess stereochemical complementarity with relation to -- the active site. The resulting increased complementarity of DANA and DANA-like molecules is reflected, for example, in a K_i value for DANA that is significantly lower (indicating higher active-site affinity) than the corresponding values for sialic acid and its derivatives. As described in greater detail below, the increased complementarity is also evidenced by <u>in vivo</u> anti-viral activity of DANA.

Accordingly, a preferred subgroup of anti-viral agents suitably used in pharmaceutical formulations of the present invention includes DANA-like molecules, especially those with a K_i of greater than 10^{-7}. More generally, 5-, 6- and 7-membered carbocyclic and heterocyclic compounds that possess the structural feature of carboxylate-planarity are preferred candidates for anti-viral agents to use in accordance with the present invention. Exemplary of such compounds are the molecules represented, respectively, by formula II. These molecules comprise a carboxylate moiety that is positioned in the plane of the ring nucleus by virtue of the sp^2-hybridized system which includes the heteroatom or C_3, as the case may be, and the carbon that bears the carboxylic-acid moiety or an analogue thereof, where

"analogue" denotes a moiety that can interact either ionically (say, charge-charge interaction) or covalently (via a Schiff reaction, for instance) with a reactable amino moiety in the active site, such as is presented by arginine 371 corresponding to the coordinates for the atoms ARG NH1 371 and ARG NH2 371 (see Figure 1).

Another group of preferred candidate anti-viral molecules is comprised of heterocyclic compounds wherein the heteroatom is oxygen, a ring carbon is present that is "anomeric", or positioned for substituent dipole:dipole interactions with the heterooxygen, and the anomeric carbon carries A-face substituents that are not subject to anomerization, i.e., substituents around this carbon atom are "non-mutarotatable." It has been found that heterocyclic compounds comprising such an anomeric carbon, which cannot undergo anomerization under physiological conditions, are more likely to possess (or to be amenable, as described above, to modifications effecting) stereochemical complementarity with the neuraminidase active site. In addition, such non-mutarotatable compounds are expected to be less susceptible to the influence of neuraminic acid-degradation pathways than known in vitro inhibitors of viral neuraminidase.

Exemplary of such heterocyclic compounds are molecules represented by formula I. In this vein, the fact that neuraminic acid has a binding affinity in the millimolar range for viral neuraminidase, and that an equilibrium mixture of neuraminic acid is mostly Â-neuraminic acid (beta:alpha = 98:2), see Kitajima et al., Biochemistry 1984 23 310, indicates that the actual affinity of the alpha form of a formula I molecule (where substituent R on the anomeric carbon extends into the plane of the paper) is on the order of 50 times greater than that of the beta form. Accordingly, a preferred subgroup of anti-viral candidate molecules within formula I includes ∝-neuraminic acid analogues that are substituted at the C_2 and C_3 carbons, respectively, so that the anomeric carbon cannot mutarotate due to steric interference or interactions between substituents and active-

site moieties which favor the non-mutarotated form. Additional modifications can also be made, for example, at C_3, C_4 or C_5.

It is known that single amino-acid changes can cause major changes in activity of influenza virus neuraminidase which are not predictable on the basis of any theoretical method. Insofar as it may not be necessary for the complementarity between compound and active site to extend over all residues of the active site, compounds that bind atoms comprising fewer than all of the residues of the active site are encompassed by the present invention.

In summary, the general principles of receptor-based drug design can be applied by persons skilled in the art, using the crystallographic data presented above, to produce compounds having sufficient stereochemical complementarity to produce a high-affinity binding of the active site of influenza virus neuraminidase.

The present invention is further described below by reference to the following, non-limiting examples.

Example 1 2-Deoxy-N-acetyl-α-D-neuraminic acid (DANA)

The simplest method of preparing this compound is by catalytic hydrogenation of 2,3-dehydro-N-acetylneuraminic acid using methods previously described by T.W. Greene, PROTECTIVE GROUPS IN ORGANIC SYNTHESIS, Wiley and Sons (1981), at pages 29-31. See Example 4 infra. Although it is possible to prepare 2-deoxy-α-D-neuraminic acid in a one-pot reaction, analogues of the general formula (I) are not so readily synthesized from this template.

Example 2 General Synthesis of Compounds of Formula I

A general synthetic route to this class of compound is described in Scheme 1, shown in Figure 4. The starting point for the preparation of C-1 substituted sugars is the glycal structure which upon treatment with hydrogen chloride followed by reaction with sodium thiophenoxide results in the formation of the thioglycoside. The thioglycoside (structure III) is converted to the corresponding sulphone (structure

IV) by oxidation with metachloroperoxybenzoic acid. The sulphone is the key intermediate in the preparation of C-1 substituted sugars, because the C-1 position is now activated towards electrophiles. Treatment of the sulphone IV with lithium diisopropyl amide followed by reaction with dimethyl carbonate yields respectable quantities of the isolable alpha and beta C-1 substituted sugars Ia.

We have extended this synthesis to the preparation of C-1 phosphorus sugars Ib by treating sulphone IV with the electrophile diethyl chlorophosphate in the presence of base. This entry into these classes of compounds provides us with very "user-friendly" templates and allows one to functionalize various centers around the carbohydrate ring. Other electrophiles may also be used, for example to make sulphur-based compounds Ic.

Example 3 Specific synthetic strategy according to Scheme 1

Figure 5 summarizes a flow sheet for synthesis of specific compounds according to the invention, utilizing the general strategy set out in Scheme 1 (Example 2 above and Figure 4). Abbreviations used are as follows:

DMF	N,N-dimethylformamide
TBDMS	tertiary butyldimethylsilyl
Ph	phenyl
Bn	benzyl

The following examples represent typical syntheses utilizing Scheme 1. Roman numerals refer to Figure 5.

Example 4 2-Deoxy-N-acetyl-α-D-neuraminic acid

The compound 2,3-dehydro-N-acetyl-D-neuraminic acid (5.8 mg) was dissolved in methanol (5 ml) and treated with PtO_2 (3 mg). The mixture was hydrogenated at 1 atmosphere and room temperature. The reaction proceeded quantitatively to yield the title compound, which had Rf on thin layer chromatography in propanol:water (3:1) of approximately 0.3. The ^1H and ^{13}C NMR data were consistent with the proposed

structure (i.e., no definite olefinic proton observed, H_{3axial} and $H_{3equatorial}$ δ 1,8 and 2,3, respectively).

Example 5 3,4,6-tri-O-acetyl-2-deoxy-ß-L-arabino-hexopyranosyl thiophenoxide

Tri-O-acetyl-L-glucal (10.64 g) was dissolved in toluene (150 ml) and cooled to -5°C. Dry HCl gas was bubbled through the solution until the starting material had been consumed, as indicated by thin layer chromatography. The solution was evaporated and the residue dissolved in N,N-dimethylformamide (DMF)(100 ml), and treated dropwise with a solution of sodium thiophenoxide (11.38 g) in DMF (60 ml) at 0°C. The mixture was refrigerated overnight and the DMF removed under high vacuum. The residue was partitioned between ice water (200 ml) and CH_2Cl_2 (200 ml). The organic layer was washed with ice water (3 x 200 ml), dried, and evaporated to give an orange oil (17 g). The crude product VIII was purified by flash chromatography in two 8.5 g batches on a 6 x 15 cm column, eluting with ethyl acetate:hexane 3:7 and taking 150 ml fractions. Those fractions with a single spot at R_f:0.27 (in the same solvent) were combined and evaporated to give a yellow oil which crystallized on standing (8.16 g, 54%). ^{1}H-NMR ($CDCl_3$): δ 1.78 (m, 1H, H_{2a}); 2.03 (m, 9H, 3xCH_3); 2.52 (m, 1H, H_{2e}); 3.68 (m, 1H, H_5); 4.18 (m, 2H, H_6x2) 4.79 (m, 3H, H_1, H_3, H_4); 7.18 (m, 5H, ArH).

Example 6 2-Deoxy-ß-L-arabinohexopyranosylthiophenoxide (Compound IX)

Compound VIII (9.6 g) was dissolved in dry methanol (200 ml) and treated with sodium (0.1 g). The mixture was left at room temperature for 2 hours and then CO_2 was bubbled through the mixture for 15 minutes. The solvent was removed and the residue crystallized. The solid was isolated by filtration with the aid of some diethyl ether, and dried under vacuum to give a light yellow solid (5.05 g, 78%). ^{1}H-NMR (D_2O): δ 1.92 (m, 2H, H_{2a}, H_{2e}), 3.70 (m, 5H, H_3, H_4, H_5, H_6x2), 4.95 (m, 1H, H_1), 7.40 (m, 5H, ArH).

Example 7 4,O-Benzyl-3,6 bis(t-butyldimethylsilyloxy)-2-deoxy-β-L-arabinohexopyranosyl thiophenoxide (Compound XI)

The hydroxy compound, Compound IX (3 g) was dissolved in DMF (60 ml) and treated with imidazole (3.51 g) and t-butyldimethylsilylchloride (3.87 g), and stirred overnight at room temperature. The solvent was removed under high vacuum and the residue partitioned between CH_2Cl_2 (150 ml) and ice water (100 ml). The organic layer was washed with ice water (3 x 100 ml), dried and evaporated to give a yellow oil (6.01 g). The oil is 3,6 bis (t-butyldimethyl-silyloxy)-2-deoxy-β-L-arabino-hexopyranosyl thiophenoxide) (Compound X).

This intermediate (5.2 g), dissolved in DMF (30 ml), was added to a suspension of NaH (0.37 g) in DMF (30 ml). The mixture was stirred for 30 min. then benzyl bromide (1.9 ml) in DMF (20 ml) was slowly added. An equivalent amount of benzyl chloride could also suitably be used. The resulting solution was stirred at room temperature for 2 hours. The solvent was removed under high vacuum and the residue dissolved in CH_2Cl_2 (150 ml) and washed with ice water (3x80 ml). The organic solution was dried and evaporated to give a yellow oil. The oil was purified by flash chromatography (6 x 12 cm), eluting with 3% ethyl acetate in hexane and taking 100 ml fractions. Those fractions with a single spot at R_f = 0.67 (10% ethyl acetate in hexane) were combined and evaporated to give a colorless oil (4.75 g, 81% overall). The intermediate hydroxy Compound X (1.48 g) was also recovered from the column. (R_f 0.41 10% Ethyl acetate in hexane)

^{1}H-NMR δ 0.10 (m, 12H, $SiCH_3$ x 4); 0.89 (m, 18H, SitBu x 2); 1.70 (ddd, 1H, $J_{2a,1a}$ 11.7, $J_{2a,2e}$ 12.0, $J_{2a,3}$ 5.14, H_{2a}); 2.22 (ddd, 1H, $J_{2e,1a}$ 1.72, $J_{2e,2a}$ 12.0, $J_{2e,3}$ 5.14, H_{2e}); 3.32 (m, 2H, H_4, H_5); 3.78 (m, 3H, H_3, H_6x2); 4.63 (d, 1H, $J_{11.07}$, CH_2Ph); 4.77 (dd, 1H, $J_{1a,2a}$ 11.7, $J_{1a,2e}$ 1.72, H_{1a}); 4.88 (d, 1H, $J_{11.07}$, CH_2Ph); 7.37 (m, 1OH, SPh, CH_2Ph).

Example 8 4-O Benzyl-3,6 bis (t-butyldimethylsilyloxy)-2-deoxy-β-L-arabinohexopyranosylphenylsulphone (Compound XII)

The sulphide, Compound XI (4.75 g) was dissolved in CH_2Cl_2 (50 ml) and added dropwise to a suspension of m-chloroperoxybenzoic acid (3.8 g) and $NaHCO_3$ (7.6 g) in CH_2Cl_2 (50 ml) at 0°C. The mixture was stirred for 1 1/2 hours and extracted with ice water (100 ml), 5% $Na_2S_2O_3$/ saturated $NaHCO_3$ 1:1 (100 ml) and ice water (100 ml). The organic solution was dried and evaporated to give an oil that crystallized on standing (4.62 g, 92%).

^{1}H-NMR ($CDCl_3$): δ -0.03 (m, 12H, $SiCH_3$x4); 0.83 (m, 18H, SitBu x 2); 1.75 (ddd, 1H, $J_{2a,2e}$ 12.0, $J_{2a,1a}$ 12.1, $J_{2a,3}$ 12.0, H_{2a}); 2.39 (ddd, 1H, $J_{2e,2a}$ 12.0, $J_{2e,1a}$ 2.0, $J_{2e,3}$ 5.0, H_{2e}); 3.13 (m, 1H, H_5), 3.33 (dd, 1H, $J_{4,5}$ 9.09, $J_{4,3}$ 9.09, H_4), 3.69 (m, 3H, H_3, H_6x2), 4.34 (dd, 1H, $J_{1a,2a}$ 12.1, $J_{1a,2e}$ 2.0, H_{1a}), 4.55 (d, 1H, J_{gem} 10.9, CH_2Ph), 4.78 (d, 1H, J_{gem} 10.9, CH_2Ph), 7.47 (m, 10H, SPh, CH_2Ph).

Example 9 α-carboxymethyl-β-phenylsulphonyl-4-O-benzyl-3,6 bis (t-butyldimethyl-silyloxy)-2-deoxy-L-arabinohexopyranose (Compound XIII)

The sulphone, Compound XII (0.5 g), was dissolved in tetrahydrofuran (3 ml) and cooled to -78°C under argon, then treated with lithium diisopropyl amide solution (0.8 ml, 1.24 M) and stirred for 5 minutes. The mixture was treated with dimethylcarbonate (1 ml) and allowed to warm to room temperature over 1 hour, then treated with saturated NH_4Cl solution (5 ml). Ether (100 ml) was added and the mixture extracted with saturated NaCl solution (2x20 ml). The organic solution was dried and evaporated. The crude material was purified on a chromatatron eluting with 5% ethyl acetate in hexane. One main band eluted from the plate after several minor bands. This band was evaporated to give the carboxy compound (0.404 g, 73%) as a colorless oil which crystallized on standing.

IR (neat): 2980, 1770, 1335, 1280, 1160, 1115, 860, 800 cm^{-1}.

^{1}H-NMR ($CDCl_3$) δ -0.04 (m, 12H, $SiCH_3x4$); 0.86 (m, 18H, SitBu x 2); 1.18 (dd, 1H, $J_{2a,2e}$ 7.2, $J_{2a,3}$ 7.2, H_{2a}); 2.50 (m, 1H, H_{2e}), 2.97 (m, 1H, H_5); 3.38 (s, 3H, OCH_3); 3.39 - 4.88 (m, 6H, H_6x2, H_4, H_3, CH_2Ph); 7.26 (m, 10H, SPh, CH_2Ph).

Example 10 Methyl 4-O-benzyl-3,6 bis (t-butyldimethyl-silyloxy)-2-deoxy-β-L-arabinohexopyranosyl carboxylate (Compound XIV)

Lithium naphthalenide solution was prepared as follows:

Naphthalene (1 g) was added to a suspension of lithium clippings (0.1 g) in tetrahydrofuran (20 ml) under argon. The mixture was stirred vigorously for 18 hours. [LiNap] = 0.393 M.

(a) From the carboxy sulphone (two step method). The second sulphone Compound XIII (0.35 g) s dissolved in tetrahydrofuran (10 ml), cooled to -90°C and treated with the LiNap solution (3.5 ml). After 10 minutes the mixture was treated with methanol (0.2 ml) at -78°C and allowed to warm to room temperature over 1 hour, then saturated NH_4Cl solution (2 ml) was added. Ether (100 ml) was added to the mixture and the solution was extracted with sat. NaCl (2x20 ml). The organic extract was dried and evaporated to give a viscous yellow oil. The crude product was purified by flash chromatography (2x15 cm) eluting with 5% ethyl acetate in hexane.

Those fractions with a single spot at R_f = 0.23 were combined and evaporated to give the alpha methyl carboxylate (0.112 g, 40%). Those fractions with a single spot at R_f = 0.11 (5% ethyl acetate in hexane) were combined and evaporated to give the beta methylcarboxylate (0.05 g, 18%).

alpha carboxy: ^{1}H-NMR ($CDCl_3$) δ -0.01 (m, 12H, $SiCH_3x4$); 0.80 (m, 18H, SitBu x 2); 1.76 (ddd, 1H, $J_{2a,2e}$ 13.2, $J_{2a,1e}$ 5.3, $J_{2a,3a}$ 10.4, H_{2a}), 2.27 (ddd, 1H, $J_{2e,2a}$ 13.2, $J_{2e,1e}$ 3.2, $J_{2e,3a}$ 3.6, H_{2a}); 3.32 (dd, 1H, $J_{4a,3a}$ 8.2, $J_{4a,5a}$ 8.2, H_{4a}); 3.58 (m, 1H, H_{5a}); 3.66 (s, 3H, OCH_3) 3.73 (m, 3H, H_{3a}, H_6x2); 4.40 (dd, 1H,

$J_{1e,2a}$ 5.3, $J_{1e,2e}$ 3.2, H_{1e}); 4.56 (d, 1H, J_{gem} 11.13, CH_2Ph); 4.74 (d, 1H, J_{gem} 11.13' CH_2Ph); 7.21 (m, 5H, $CH_2\underline{Ph}$).

beta carboxy: ^{1}H-NMR δ -0.02 (m, 12H, $SiCH_3$x4); 0.78 (m, 18H, SitBu x 2); 1.62 (ddd, 1H, $J_{2a,2e}$ 11.5, $J_{2a,1a}$ 12.1, $J_{2a,3e}$ 11.5, H_{2a}); 2.10 (ddd, 1H, $J_{2e,2a}$ 11.5, $J_{2e,1a}$ 2.17, $J_{2e,3a}$ 5.0, H_{2e}); 3.15 (ddd, 1H, $J_{5a,4a}$ 9.4, $J_{5a,6a}$ 3.0, $J_{5a,6b}$ 3.0, H_{5a}); 3.29 (dd, 1H, $J_{4a,3a}$ 9.4, $J_{4a,5a}$ 9.4, H_{4a}); 3.67 (s, 3H, OCH_3); 3.74 (m, 3H, H_{3a}, H_6x2); 4.79 (d, 1H, J_{gem} 10.9, CH_2Ph), 7.21 (m, 5H, $CH_2\underline{Ph}$).

Example 11 4-O-benzyl-3,6 bis (t-butyldimethylsilyloxy-2-deoxy-α-L-arabinohexepyranosyl carboxylate

As will be readily appreciated by those skilled in the art, the alpha and beta forms of Compound XIV can be deesterified by treatment with base, utilizing conditions previously described. See Greene, op. cit., at pages 158-159.

Example 12 Alternative method of synthesis

The C-1 carbanion generated by reduction of the corresponding C-1 chloro compound can be quenched with an appropriate electrophile to produce a desired compound of general formula I. An exemplary synthesis along these lines is illustrated below:

Compound II ----------> Compound VII
(Fig. 4) HCl gas (Fig. 5)

Compound VII ----------> Li salt of VII
Li naphthalenide

Li salt of VII ----------> 2-deoxy-α-D-neuraminic acid
electrophile

Example 13

(a) Preparation of Methyl N-acetyl-D-neuraminate (2)

N-acetylneuraminic acid (100 mg, 0.32 mmol) was stirred in anhydrous methanol (25 ml) containing Dowex 50X8 (H^+) (25 mg) at room temperature for 16 hours. Thin layer chromatography of the reaction mixture (ethyl acetate/methanol/water: 10/4/1) indicated that the reaction

was complete (product R_f 0.50). The reaction mixture was filtered and the resin washed with methanol (10 ml x 2). The filtrate and washings were combined and concentrated to dryness to afford a white crystalline powder (102 mg, 98%).

^{1}H-NMR (D_2O) δ 3.82 (s, 3H, $COOCH_3$).

The rest of the spectrum was identical to that previously reported. See Ogura et al. (1986), op. cit.

(b) Preparation of Methyl N-Acetyl-4,7,8,9-tetra-O-acetyl-2β-chloro-2-deoxy-D-neuraminate (3)

Compound (2) (100 mg, 0.32 mmole) was stirred with acetyl chloride (5 ml) at room temperature for 60 hours. The solution was evaporated to dryness, taken up in anhydrous benzene (20 ml x 3) and concentrated to a white foam powder (130 mg, 0.255 mole).

^{1}H-NMR indicated the title compound to be the only product present and to be identical with that previously reported by Ogura et. al., Carbohydr. Res. 1986 158 37. The literature also describes other methods for the preparation of certain other glycosyl halides, and these methods are adequate to obtain reasonable amounts of those compounds. See, e.g., Kuhn et al., Chem. Ber. 1966 99 611; Warner & O'Brien, Biochemistry 1979 18 (13) 2783; Ogura et al., loc. cit.; Okamoto et al., Bull. Chem. Soc. Japan 1987 60 631.

(c) Preparation of Methyl N-acetyl-4,7,8,9-tetra-O-acetyl-2-deoxy-2α-allylthio-neuraminate (4)

Compound (3) (500 mg, 0.98 mmole) was dissolved in anhydrous N,N-dimethylformamide (5 ml), treated with sodium allylthiolate (136 mg, 1.08 mmole), and stirred at room temperature under nitrogen for 48 hours. The reaction mixture was concentrated to dryness under high vacuum. The residue was partitioned between ethyl acetate (50 ml) and 5% sodium hydrogen carbonate solution (25 ml). The organic phase was separated and washed with 10% sodium chloride solution, dried over anhydrous sodium sulphate, then evaporated to dryness to afford a crude product which was

purified by flash-column chromatography (silica gel, ethyl acetate as eluting solvent) to give the title compound (3) (200 mg, 37.3%) ^{1}H-NMR ($CDCl_3$): δ 1.86-2.16 (dd, 5_8, $H_{3ax'}$, NAc, 4xAc, 16H, $J_{3ax,eq}$ 12.7 Hz, $H_{3ax,4}$ 11.4 Hz), 2.72 (dd, 1H, $J_{3eq,3ax}$ 12.7 Hz, $H_{3eq,4}$ 4.68 Hz, H_{3eq}); 3.34 (m, 2H, SCH_2); 3.79 (s, 3H, OCH_3); 3.89 (dd, 1H, $J_{6,5}$ 10.57 Hz, $H_{6,7}$ 2.04 Hz, H_6); 4.07 (ddd, 1H, $J_{5,6}$ 10.57 Hz, $H_{5,4}$ 11.4 Hz, $H_{5,NH}$ 9.95 Hz, H_5); 4.13 (dd, 1H, $J_{9,8}$ 5.46 Hz, $H_{9,9'}$ 12.52 Hz, H_9); 4.35 (dd, 1H, $J_{9',9}$ 12.52 Hz, $H_{9',8}$ 2.53 Hz, $H_{9'}$); 4.86 (ddd, 1H, $J_{4,3ax}$ 11.4 Hz, $H_{4,5}$ 11.4 Hz, $H_{4,5}$ 4.68 Hz, H_4); 5.09 (d, 1H, olefinic J_{cis} 9.92 Hz); 5.2 (dd, 1H, olefinic J_{trans} 16.97 Hz, allylic 1.43 Hz); 5.33 (dd, 1H, $J_{7,6}$ 1.9 Hz, $H_{7,8}$ 7.8 Hz, H_7); 5.39 (m, 1H, H_8); 5.59 (d, 1H, $J_{NH,5}$ 9.95 Hz, NH); 5.76 (m, 1H J_{CH2}, olefinic, 6.4 Hz)

(d) <u>Preparation of Sodium N-acetyl-2-deoxy-2α-allylthioneuraminate(5)</u>

Compound (4) (200 mg, 0.36 mmole) was dissolved in anhydrous methanol (20 ml) containing sodium methoxide (20 mg, 0.37 mmole). The solution was stirred at room temperature for two hours before a mixture of mixed-bed resin AG 501X 8 (50 mg) and Dowex 50X 8 (H^+) (25 mg) was added. The mixture was stirred for a further 30 minutes and then was filtered. The resins were washed with methanol (5 ml X 2) and the filtrate and washings were combined and concentrated to dryness. The residue was taken up in water (10 ml), adjusted to Ph 13 by the addition of 0.1N NaOH and stirred for 2 hours at room temperature. The solution was then adjusted to pH 6.5 by stirring with Dowex 50 X 8 (H^+) resin. Following filtration the reaction mixture was lyophilized to afford the title compound (120 mg, 85%).

^{1}H-NMR (D_2O) δ 1.79 (dd, 1H, $J_{3ax,3eq}$ 12.6 Hz, $J_{3ax,4}$ 11.4 Hz, H_{3ax}), 2.02 (s, 3H, N-Ac), 2.79 (dd, 1H, $J_{3eq,3ax}$ 12.6 Hz, $H_{3eq,4}$ 4.57 Hz, H_{3eq}), 3.37 (m, 2H, SCH_2); 3.5-3.89 (m, 7H, H_4, H_5, H_6, H_7, H_8, H_9, $H_{9'}$), 5.10 (d, 1H, olefinic J_{cis} 9.94 Hz); 5.22 (dd, 1H, olefinic J_{trans}17 Hz, allylic 1.35 Hz); 5.84-6.0 (m, 2H, NH, H, olefinic).

This procedure is summarized in Figure 6.

Example 14 Second General Reaction Scheme

Example 13 represents a specific instance of the general reaction scheme which is summarized in Figure 3, in which the substituents R^1 to R^5 are as defined in general formula I, R in compound 3 is as defined in general formula III, while R in compounds 4 and 5 is as defined in general formula I. Designations of compounds in Examples 15 to 17 are as in Figure 5.

The scheme comprises the steps of:

preparing an alkyl N-acetyl neuraminate,

reacting said alkyl N-acetyl neuraminate with an alcohol in the presence of an acid catalyst to yield the corresponding ester,

acylating and halogenating the ester by reaction with an acyl chloride,

treating the halogenated and acylated ester with a nucleophile to effect halogen-nucleophile exchange, deacylating and de-esterifying the resulting compound, and recovering the compound of general formula I.

Thus, in Example 13 the treatment of compound (1) with an alcohol in the presence of an acid catalyst yielded the corresponding ester in good yield (compound (2)). Acylation and halogenation of compound (2) was achieved through reaction with the appropriate acyl chloride, resulting in the formation of compound (3). Halogen-nucleophile exchange was achieved by treatment of compound (3) with the appropriate nucleophile to yield compound (4). Deacylation and deesterification by treatment of compound (4) under hydrolytic conditions resulted in the formation of compound (5).

Example 15 Preparation of Methyl N-Acetyl-4 7,8,9-tetra-O-acetyl-2-deoxy-2α-fluoro-D-neuraminate (4)

Compound (3) (130 mg, 0.255 mmole) was dissolved in anhydrous acetonitrile (50 ml), treated with silver fluoride (130 mg, 1.025 mmole), stirred at room temperature under nitrogen, and protected from light for 72 hours. Two major components were isolated from the reaction mixture (thin

layer chromatography; ethyl acetate, R_f 0.45 and 0.30) by flash chromatography. Compound (3) was identified as the slower moving compound by NMR spectroscopy.

^{1}H-NMR ($CDCl_3$), δ 1.7 (m,1H,H_{3ax}), 2.0-2.2 (m,15H,acetyl-CH_3 X5), 2.6 (m,1H,H_{3eq}), 3.72 (s,3H,$COOCH_3$), 4.10-4.20 (m,2H,H_5 and H_9), 4.20-4.30 (m,1H,H_6), 4.45-4.55 (m,1H,$H_{9'}$), 5.05-5.10 (m,1H,H_4), 5.35-5.45 (m,3H,H_7,H_8, and NH)

^{19}F-NMR ($CDCl_3$, δ 1,1',2,2'-tetrachloro-3,3', 4,4'-tetrafluorocyclobutane as external reference) -2.5 - -3.0

Example 16 Preparation of Sodium N-acetyl-2-deoxy-2α-fluoro-neuraminate (5)

Compound (4) was dissolved in anhydrous methanol (5 ml) containing sodium methoxide (2 mg). The solution was stirred at room temperature for 40 min before a mixture of mixed-bed resin AG 501X 8 (5 mg) and Dowex 50X 8 (H^+) (2.5 mg) was added. The mixture was stirred for a further 30 minutes and then was filtered. The resins were washed with methanol (2 ml x 2) and the filtrate and washings were combined and concentrated to dryness. The residue was taken up in water (10 ml), adjusted to pH 11.8 by the addition of 0.1N NaOH and stirred for 1 hour at room temperature. The solution was then adjusted to pH 6.5 by stirring with Dowex 50X 8 (H^+) resin. Following filtration the reaction mixture was lyophilized to afford the title compound (5 mg) as a white powder.

^{1}H-NMR (D_2O) δ 1.7-1.9 (m,1H,H_{3ax}), 2.1 (s, 3H, acetyl-CH_3), 2.9-3.0 (m,1H,H_{3eq}), 3.5-4.1 (m,7H,H_4,H_5,H_6,H_7,H_8,H_9,$H_{9'}$)

Example 17 Third general method of synthesis

Catalytic hydrogenation of the ß-chlorosialic acid can be achieved, as described in Example 18 for a typical case. The ß-chloroneuraminic acid is prepared along the lines of Example 13(b) above. The method is modified from

that of Schmid, Christian and Zbiral, Tetrahedron Letters 1988 29 3643-3646. The N-acetylneuraminic acid or analogues thereof used as starting materials for preparation of the ß-chloro compounds may be synthesized using N-acetylneuraminic acid aldolase (E.C.4.1.3.3) See, e.g., Bednarski et al., J. Am. Chem. Soc. 1987 109 1283; Augé et al., Tetrahedron Letters 1984 25 4663-4664.

Example 18 Preparation of 2-deoxy-N-acetyl-α-D-neuraminic acid by catalytic hydrogenation

Methyl-N-acetyl-4,7,8,9-tetra-O-acetyl-2 chloro-2-deoxy-D-neuraminate (2.0 g) was dissolved in toluene (30 ml) and Pd/C (10%, 0.91 g) and pyridine (0.6 ml) were added. The mixture was hydrogenated at 50 psi for 18 hrs. Insoluble solid was filtered off and washed with toluene (40 ml x 3) and methanol (40 ml x 2). The combined filtrate and washings were evaporated to dryness. The residue was dissolved in ethyl acetate (150 ml), and this solution washed with 5% sodium chloride solution (50 ml), dried over calcium chloride and evaporated affording the crude compound (1.76 g). Purification by column chromatography using ethyl acetate as solvent gave 1.0 g of 2-deoxy-N-acetyl-α-D-neuraminic acid.

Example 19 Preparation of Sodium 2,3-dideoxy-α-D-galacto-2-octulosonate

This compound was prepared using catalytic hydrogenation as described in Examples 17 and 18, followed by deacylation/deesterification as broadly described in Example 13(d).

^{1}H-NMR (D_2O, DSS as internal standard)

δ (ppm): 1.77 (ddd, 1H, $J_{3a,3e}$ -12.0, $J_{3a,4}$ 11.7, $J_{3a,2}$ 6.4, H_{3a}); 2.44 (dd, 1H, $J_{3e,3a}$ -12.0, $J_{3e,4}$ 2.6, H_{3e}); 3.4-4.1 (m, 5H, H_5, H_6, H_7, H_8 & $H_{8'}$); 4.32 (d, 1H, $J_{1e,3a}$ 6.4, H_1).

Example 20 Preparation of Sodium 2,3,5-trideoxy-5-acetamido-α-D-galacto-2-octulosonate

This compound was prepared using catalytic hydrogenation as described in Examples 17 and 18, followed by deacylation/deesterification as broadly described in Example 13(d).

^{1}H-NMR (D_2O, DSS as internal standard).

δ (ppm): 1.82 (ddd, 1H, $J_{3a,3e}$ -13.1, $J_{3a,4}$ 11.9, $J_{3a,e}$ 6.2, H_{3a}); 2.02 (s, 3H, CH_3CO); 2.49 (dd, 1H, $J_{3e,3a}$ - 13.1, $J_{3e,4}$ 4.2, H_{3e}); 3.5-3.9 (m, 5H, H_5, H_6, H_7, H_8 & $H_{8'}$); 4.44 (d, 1H, $J_{2,3a}$ 6.2, H_2).

Example 21 Inhibition of influenza virus neuraminidase

An in vitro bioassay of the above-described compounds against N2 influenza virus neuraminidase was conducted, following Warner and O'Brien, Biochemistry 1979 18 2783-2787. For comparison, with the same assay the K_i for the compound of Example 1, 2-deoxy-N-acetyl-α-D-neuraminic acid, was determined to be 3 X 10^{-4} M.

Values for K_i were measured via a spectrofluorometric technique which uses the fluorogenic substrate 4-methylumbelliferyl N-acetylneuraminic acid (MUN), as described by Meyers et al., Anal. Biochem. 1980 101 166-174. For both enzymes, the assay mixture contained test compound at several concentrations between 0 and 2 mM, and approximately 1 mU enzyme in buffer (32.5 mM MES, 4 mM $CaCl_2$, pH 6.5 for N2; 32.5mM acetate, 4 mM $CaCl_2$, pH 5.5 for V. cholerae neuraminidase).

The reaction was started by the addition of MUN to final concentrations of 75 or 40 mM. After 5 minutes at 37°C, 2.4 ml 0.1 M glycine-NaOH, pH 10.2 was added to 0.1 ml reaction mixture to terminate the reaction. Fluorescence was read at excitation 365 nm, emission 450 nm, and appropriate MUN blanks (containing no enzyme) were subtracted from readings. The K_i was estimated by Dixon plots (1/fluorescence versus compound concentration). Results are summarized in Table 2.

Table 2

Inhibition of influenza virus neuraminidase in vitro

Compounds	K_i(M)
2-deoxy-N-acetyl-α-D-neuraminic acid	3×10^{-4}
sodium 2,3-dideoxy-α-D-galacto-2-octulosonate	1×10^{-3}
sodium 2,3,5-trideoxy-5-acetamido-α-D-galacto-2-octulosonate	5×10^{-5}
2,3-dideoxy-α-D-glycero-D-galacto-2-nonulosonic acid	2×10^{-2}
2-α-fluoro-N-acetylneuraminic acid	4×10^{-5}
sodium N-acetyl-2-deoxy-2α-allyl-thioneuraminate	1×10^{-5}

Example 22 In vivo anti-viral activity

The compound DANA (2-deoxy-N-acetyl-α-D-neuraminic acid), which was shown in Example 23 to have anti-neuraminidase activity in vitro, was tested for anti-viral activity in an in vivo assay. When administered intranasally to mice before and during challenge with influenza A virus, this compound reduced the titre of virus in lung tissue 1 to 3 days after infection.

Mice were infected intranasally with 50 µl of 10^3 $TCID_{50}$ units/mouse of H2N2 influenza A virus (A/Sing/1/57). The compound was administered intranasally at a dose rate of either 25 mg/kg body weight or 100 mg/kg body weight (50 µl of aqueous solution/mouse) as follows: 24 hours and 3 hours before infection; 3 hours after infection; then twice daily on each of days 1, 2 and 3 after infection.

The mice were sacrificed on days 1, 2 and 3 after infection, their lungs removed and virus titres in the lungs measured. The titres were plotted graphically and expressed as the areas under the curves (AUC). Results are summarized below.

Table 3

Dose of compound (mg/kg body weight)	Virus titre (AUC) compared to untreated infected mice
25	57%
100	19%

In light of the fact that FANA was hitherto thought to be inactive in vivo, see Palese and Schulman, op. cit., the high antiviral activity revealed when DANA was administered intranasally to mice is especially surprising. It appears that the route of administration may be significant in this regard, since DANA is rapidly excreted when given by other routes. See Nhle et al., Eur. J. Biochem. 1982 126 543-48.

Pharmaceutical Compositions

A pharmaceutical formulation within the present invention combines, with an active agent that binds the viral neuraminidase active site and displays in vivo anti-viral activity, a carrier for the active agent which is pharmaceutically acceptable. A pharmaceutically acceptable carrier is a solid, liquid or gaseous material that can be used as a vehicle for administering a medicament because the material is inert or otherwise medically acceptable, as well as compatible with the active agent, in a particular context of administration. In addition to a suitable excipient, a pharmaceutically acceptable carrier can contain conventional additives like diluents, adjuvants, antioxidants, dispersing agents and emulsifiers, anti-foaming agents, flavor correctants, preservatives, solubilizing agents and colorants.

The nature of the excipient used with an anti-viral agent, pursuant to the present invention, is largely a function of the chosen route of administration, as discussed, for example, in REMINGTON'S PHARMACEUTICAL SCIENCES (E.W. Martin ed.) and in PHARMACEUTICAL DOSAGE FORMS AND THEIR USE (H. Hess ed.) Hans Huber Publ., 1985, the respective contents of which are hereby incorporated by reference. Preferably, the pharmaceutical compositions of the present invention are provided in a unitary-dosage form which is suitable for administration intranasally, orally, buccally or sublingually.

In accordance with the present invention, a pharmaceutical composition is advantageously delivered to the throat, nasal cavity or lungs, the intranasal route of administration being especially preferred. Delivery of an active agent to the nasal cavity can be achieved with preparations of the present invention that take the form, for example, of an aerosol or vapor, a nasal spray or nose drops, or an inhalation powder. For these applications, it may be appropriate for the active agent to be micronized, for example, to a particle size on the order of 5 microns or less.

Suitable means for effecting delivery by direct application to the mucosal lining or via inhalation are well known to the art, for example, in the context of treating asthma. In this category are squeeze-bottle devices (nebulizers) and pressurized packs, for delivering a solution of the active agent as a spray into the nose, and conventional insufflators like the Spinhaler turbo-inhaler and liquid aerosol "puffers" (Spinhaler is a registered trade mark of Fisons Corporation), which deliver metered doses of a pharmaceutical preparation.

If the active agent is delivered from solution, as would typically be the case for a nasal spray or nose drops, the carrier preferably comprises distilled water that is both sterile and substantially free of fever-inducing (pyrogenic) substances, thereby to minimize the incidence of medical complications relating to contamination. Suitable propellants to comprise carriers for use in administration by pressurized aerosol are well known, including halogenated fluorocarbon gases, carbon dioxide, and nitrogen. See, e.g., Lachman et al. in THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY (Lea and Febiger, Philadelphia), 1976. In addition, a carrier for administration via intranasal delivery or insufflation may contain oleic acid or some other pharmaceutically acceptable stabilizer, as well as a surface-active agent, e.g., a detergent like Tween 80 or Span 80, in order to enhance uptake of the active agent.

Conventional forms which are favored for oral administration include lozenges and pastilles, sublingual and buccal tablets, and oral sprays. Numerous carriers suitable for these forms are known, including solid pulverulent carriers comprising a simple sugar or corresponding alcohol (lactose, saccharose, sorbitol, mannitol, etc), a starch such as potato starch, corn starch or amylopectin, cyclodextrin, a cellulose derivative, and gelatine. Liquid carriers can also be employed to form suspensions, syrups, elixirs and solutions containing the active agent. Non-aqueous vehicles which are suitable as liquid carriers in this regard include

almond oil and other edible oils, fractionated coconut oil, oily esters, propylene glycol and ethyl alcohol.

In formulating a pharmaceutical preparation of the present invention for oral administration, a solid carrier would typically be mixed with a lubricant, such as magnesium stearate, calcium stearate or a polyethylene glycol wax, and then compressed into tablet form. In keeping with common practice, tablets can be coated with a concentrated sugar solution which may contain components like gum arabic, gelatine, talcum and titanium dioxide. Alternatively, tablets can be coated with a lacquer dissolved in a readily volatile organic solvent.

A pharmaceutical composition within the present invention contains a virus-inhibiting amount of an active agent as described above. The optimum dosage of the active compound will vary with the particular case, and can be determined routinely in the clinical context, which may be prophylactic or therapeutic. 'Prophylactic' treatment is to be understood to mean treatment intended to prevent or retard second-cycle infection as defined below, thus preventing the establishment of the complete clinical manifestations of the disease caused by that virus. 'Therapeutic' treatment is to be understood to mean treatment intended to alleviate the symptoms and severity of infection which is already established, by disrupting release of virus particles and thus preventing further cycles of viral replication. Generally, the amount of active agent present in a pharmaceutical composition of the present invention should be sufficient to inhibit at least second-cycle infection by orthomyxovirus or paramyxovirus in an animal. That is, an initial viral infection of a cell culminates in the assembly and budding of virus particles at the cell-membrane surface, which would be followed in the normal course by release of the particles and infection thereby ("second-cycle infection") of other cells. A suitable amount of active agent to include in a pharmaceutical composition of the present invention would thus retard at least this second cycle of infection by virus, it is thought by inhibiting the

action of neuraminidase that results in release of virus particles from the membrane surface.

For administration by inhalation, the daily dosage as employed for treatment, according to the present invention, of an adult human of approximately 70 kg body weight will range from 1mg to 1000 mg, preferably between 5 mg and 500 mg, and may take the form of single or multiple doses, e.g., one to six times a day. For oral administration, the daily dosage (again, for treatment of a 70 kg adult) will typically range from about 1 mg to 5 g, preferably between 5 mg and 2 g, and may be given, for example, in single to four doses per day. It will therefore be convenient for a pharmaceutical composition of the present invention to contain active (antiviral) agent at a concentration in the range of 0.000001 to 100 mg/ml.

Other objects, features and advantages of the present invention will become apparent from the preceding detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

What Is Claimed Is:

1. A pharmacologically active composition comprising:

(i) a virus-inhibiting amount of a compound that binds the active site of influenza virus neuraminidase and that displays in vivo activity against orthomyxovirus or paramyxovirus; and

(ii) a pharmaceutically-acceptable carrier for said compound.

2. A pharmacologically active composition according to Claim 1, wherein said carrier is suitable for intranasal administration.

3. A pharmacologically active composition according to Claim 2, wherein (a) said compound is micronised and (b) said carrier comprises a propellant suitable for pressurized aerosol administration.

4. A pharmacologically active composition according to Claim 3, wherein said carrier further comprises a fatty acid, a surface-active agent or a detergent.

5. A pharmacologically active composition according to Claim 2, wherein said compound and carrier form a solution or a suspension of said compound in said carrier, said solution or suspension being suitable for administration directly to nasal mucosa.

6. A pharmacologically active composition according to Claim 1, wherein said carrier is sterile water that is substantially pyrogen-free.

7. A pharmacologically active composition according to Claim 1, wherein said compound displays in vivo activity against a virus selected from the group consisting of influenza virus, parainfluenza virus, mumps virus, Newcastle disease virus, fowl plague virus and Sendai virus.

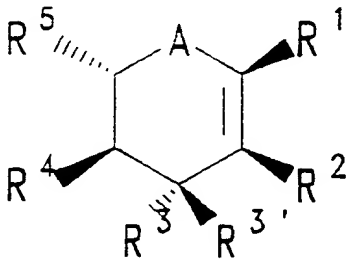
8. A pharmacologically active composition according to Claim 7, wherein said virus is an influenza virus.

9. A pharmacologically active composition according to Claim 1, wherein said compound possesses a K_i value, with respect to said active site, of less than 10^{-7} M.

10. A pharmacologically active composition according to Claim 9, wherein said K_i value is less than about 0.5×10^{-6} M.

11. A pharmacologically active composition according to Claim 1, wherein said compound is a carbocyclic or heterocyclic compound comprised of a 5-, 6- or 7-membered ring carrying a substituent selected from a carboxylate moiety and an analogue thereof, said ring and said substituent being positioned in the same plane.

12. A pharmacologically active composition according to Claim 11, wherein said compound is represented by the structural formula



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wherein

A denotes O,

R^1 denotes COOH, $P(O)(OH)_2$, NO_2, SOOH, SO_3H, tetrazol, CH_2CHO, CHO, $CH(CHO)_2$ or, where R^1 is COOH, $P(O)(OH)_2$, SOOH or SO_3H, an ethyl, methyl or pivaloyl ester thereof,

R^2 denotes H, OR^6, F, Cl, Br, CN, NHR^6, SR^6 or CH_2X, wherein X is NHR^6, halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; or an unsubstituted aryl group or an aryl substituted by a halogen, an allyl group, an OH group, an NO_2 group, an NH_2 group or a COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, $N(R^6)_2$, SR^6 or OR^6,

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R^4 denotes $NHC-R^7$, where R^7 is an unsubstituted or halogen-substituted linear or cyclic alkyl group of 1 to 6 carbon atoms, or SR^6, OR^6, COOH or alkyl/aryl ester thereof, NO_2, $C(R^6)_3$, CH_2COOH or alkyl/aryl ester thereof, CH_2NO_2 or CH_2NHR^7, and

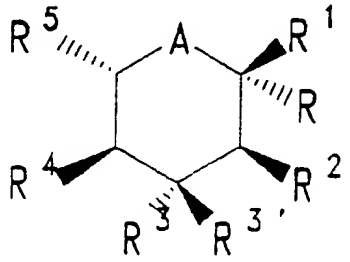
R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$ where Y is O, S or H, and successive Y moieties in an R^5 group are the same or different.

13. A pharmacologically active composition according to Claim 12, wherein said compound is DANA or FANA.

14. A pharmacologically active composition according to Claim 1, wherein said compound is a heterocylic compound comprising a heterooxygen and an anomeric carbon carrying substituents that are non-mutarotatable.

15. A pharmacologically active composition according to Claim 14, wherein said compound is a C9-carbohydrate.

16. A pharmacologically active composition according to Claim 1, wherein said compound is represented by the structural formula



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wherein

A denotes O,

R denotes hydrogen, CN, $CH-NHR^6$, CH_2OR^6, CH_2F, CH_3, $Sn(R^6)_3$, $Si(R^6)_3$ or SR^7, where R^7 is an alkyl group which has an alkyl chain of 1 to 6 carbons; or an aryl group wherein the aryl moiety is mono-, di- or tri-substituted with halogen, amino, hydroxyl or carboxyl,

R^1 denotes COOH, $P(O)(OH)_2$, NO_2, SOOH, SO_3H, tetrazole, CH_2CHO, CHO, $CH(CHO)_2$ or, where R^1 is COOH, $P(O)(OH)_2$, SOOH or SO_3H, an ethyl, methyl or pivaloyl ester thereof,

R^2 denotes H, OR^6, F, Cl, Br, CN, NHR^6, SR^6 or CH_2X, wherein X is NHR^6, halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; or an unsubstituted aryl group or an aryl substituted by a halogen, an allyl group, an OH group, an NO_2 group, an NH_2 group or a COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, $N(R^6)_2$, SR^6 or OR^6,

R^4 denotes $NHC-R^7$ (with O), where R^7 is an unsubstituted or halogen-substituted linear or cyclic alkyl group of 1 to 6 carbon atoms, or SR^6, OR^6, COOH or alkyl/aryl ester thereof, NO_2, $C(R^6)_3$, CH_2COOH or alkyl/aryl ester thereof, CH_2NO_2 or CH_2NHR^7, and

R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$ where Y is O, S or H, and successive Y moieties in an R^5 group are the same or different.

17. A pharmacologically active composition according to Claim 16, wherein said compound is selected from the group consisting of 2-deoxy-N-acetyl-α-D-neuraminic acid, methyl N-acetyl-4,7,8,9-tetra-O-acetyl-2-deoxy-2α-allylthio-neuraminate, sodium N-acetyl-2-deoxy-2α-allylthioneuraminate, methyl N-acetyl-4,7,8,9-tetra-O-acetyl-2-deoxy-2α-fluoro-D-neuraminate and sodium N-acetyl-2-deoxy-2α-fluoro-D-neuraminate.

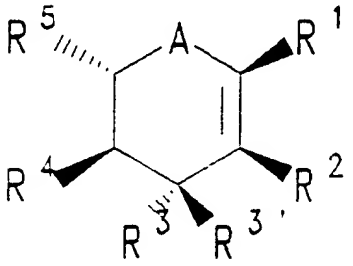
18. A compound that binds the active site of influenza virus neuraminidase and that displays <u>in vivo</u> activity against orthomyxovirus or paramyxovirus, wherein said compound is not one selected from the group consisting of the compounds set out in Table 1.

19. A compound according to Claim 18, wherein said compound binds said active site with a K_i value of less than 10^{-7} M.

20. A compound according to Claim 19, wherein said K_i value is less than about 0.5×10^{-6} M.

21. A compound according to Claim 18, wherein said compound is a carbocyclic or heterocyclic compound comprised of a 5-, 6- or 7-membered ring carrying a substituent selected from a carboxylate moiety and an analogue thereof, said ring and said substituent being positioned in the same plane.

22. A compound according to Claim 21, wherein said compound is represented by the structural formula:



II

wherein

A denotes O,

R^1 denotes COOH, $P(O)(OH)_2$, NO_2, SOOH, SO_3H, tetrazol, CH_2CHO, CHO, $CH(CHO)_2$ or, where R^1 is COOH, $P(O)(OH)_2$, SOOH or SO_3H, an ethyl, methyl or pivaloyl ester thereof,

R^2 denotes H, OR^6, F, Cl, Br, CN, NHR^6, SR^6 or CH_2X, wherein X is NHR^6, halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; or an unsubstituted aryl group or an aryl substituted by a halogen, an allyl group, an OH group, an NO_2 group, an NH_2 group or a COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, $N(R^6)_2$, SR^6 or OR^6,

O

R^4 denotes NHC-R^7, where R^7 is an unsubstituted or halogen-substituted linear or cyclic alkyl group of 1 to 6 carbon atoms, or SR^6, OR^6, COOH or alkyl/aryl ester thereof,

NO_2, $C(R^6)_3$, CH_2COOH or alkyl/aryl ester thereof, CH_2NO_2 or CH_2NHR^7, and

R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$ where Y is O, S or H, and successive Y moieties in an R^5 group are the same or different,

subject to the provisos that

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, then said compound cannot have both

(a) an R^2 that is hydrogen and

(b) an R^4 that is NH-acyl,

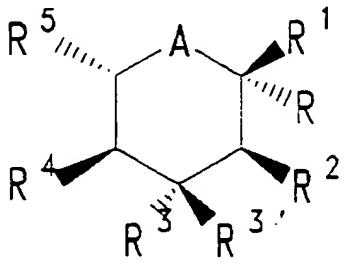
and

(ii) R^6 represents a covalent bond when Y is hydrogen.

23. A compound according to Claim 18, wherein said compound is a heterocyclic compound comprising a heterooxygen and an anomeric carbon carrying substituents that are non-mutarotatable.

24. A compound according to Claim 23, wherein said compound is a C9-carbohydrate.

25. A compound according to Claim 18, wherein said compound is represented by the structural formula



I

wherein

A denotes O,

R denotes hydrogen, CN, CH-NHR^6, CH_2OR^6, CH_2F, CH_3, $Sn(R^6)_3$, $Si(R^6)_3$ or SR^7, where R^7 is an alkyl group which has an alkyl chain of 1 to 6 carbons; or an aryl group wherein the aryl moiety is mono-, di- or tri-substituted with halogen, amino, hydroxyl or carboxyl,

R^1 denotes COOH, $P(O)(OH)_2$, NO_2, SOOH, SO_3H, tetrazole, CH_2CHO, CHO, $CH(CHO)_2$ or, where R^1 is COOH,

$P(O)(OH)_2$, SOOH or SO_3H, an ethyl, methyl or pivaloyl ester thereof,

R^2 denotes H, OR^6, F, Cl, Br, CN, NHR^6, SR^6 or CH_2X, wherein X is NHR^6, halogen or OR^6 and

R^6 is hydrogen; an acyl group having 1 to 4 carbon atoms; a linear or cyclic alkyl group having 1 to 6 carbon atoms, or a halogen-substituted analogue thereof; or an unsubstituted aryl group or an aryl substituted by a halogen, an allyl group, an OH group, an NO_2 group, an NH_2 group or a COOH group,

R^3 and $R^{3'}$ are the same or different, and each denotes hydrogen, $N(R^6)_2$, SR^6 or OR^6,

R^4 denotes $NHC(=O)-R^7$, where R^7 is an unsubstituted or halogen-substituted linear or cyclic alkyl group of 1 to 6 carbon atoms, or SR^6, OR^6, COOH or alkyl/aryl ester thereof, NO_2, $C(R^6)_3$, CH_2COOH or alkyl/aryl ester thereof, CH_2NO_2 or CH_2NHR^7, and

R^5 denotes CH_2YR^6, $CHYR^6CH_2YR^6$ or $CHYR^6CHYR^6CH_2YR^6$ where Y is O, S or H, and successive Y moieties in an R^5 group are the same or different, subject to the provisos that

(i) when R^3 or $R^{3'}$ is OR^6 or hydrogen, then said compound cannot have both

(a) an R^2 that is hydrogen and

(b) an R^4 that is NH-acyl,

(ii) R^7 is not CH_3, CH_2CH_3, phenyl, glucosyl, galactosyl, mannosyl, acetyl, benzoyl, cyclohexyl or substituted cyclohexyl and

(iii) R^6 represents a covalent bond when Y is hydrogen.

26. A compound according to Claim 25, wherein said compound is methyl N-acetyl-4,7,8,9-tetra-O-acetyl-2-deoxy-2α-allylthioneuraminate or sodium N-acetyl-2-deoxy-2α-allylthioneuraminate.

27. A method of preventing or ameliorating the symptoms of an orthomyxovirus or paramyxovirus infection, comprising

the step of administering to an animal a pharmacologically active composition comprising:

(i) a virus-inhibiting amount of a compound that binds the active site of influenza virus neuraminidase and that displays anti-orthomyxovirus or paramyxovirus activity; and

(ii) a pharmaceutically acceptable carrier for said compound.

28. A method according to Claim 27, wherein the virus is selected from the group consisting of influenza virus, parainfluenza virus, Sendai virus and mumps virus, and the animal is a human.

29. A method according to Claim 27, wherein the virus is Newcastle disease virus or fowl plague virus, and the animal is a bird.

30. A method according to Claim 27, wherein the substance is administered orally, intranasally, buccally, or sublingually.

31. A method according to Claim 27, wherein the substance is administered intranasally.

32. A method of synthesis of a compound according to general formula I, as defined in Claim 25, comprising the steps of:

providing an alkyl N-acetyl neuraminate,

reacting said alkyl N-acetyl neuraminate with an alcohol in the presence of an acid catalyst to yield the corresponding ester,

acylating and halogenating the ester by reaction with an acyl halide,

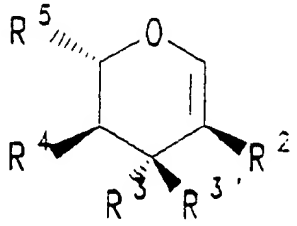
treating the halogenated and acylated ester with a nucleophile to effect halogen-nucleophile exchange,

deacylating and de-esterifying the resulting compound under hydrolytic conditions, and

recovering the compound of general formula I.

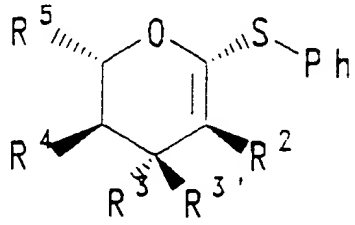
33. A method of synthesis of a desired compound of general formula I, as defined in Claim 25, which comprises the steps of:

(a) treating a glycal of formula (i)



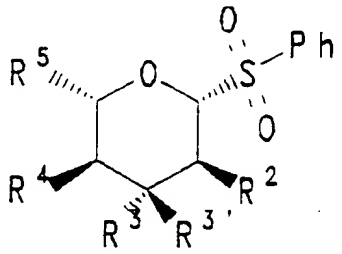
(i)

with hydrogen chloride and then with sodium thiophenoxide to form a thioglycoside of formula (ii)



(i i)

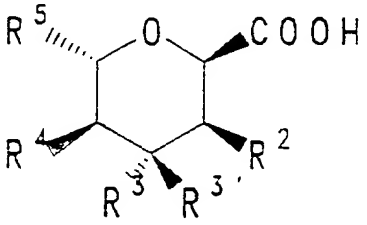
(b) oxidizing the thioglycoside with metachloroperoxybenzoic acid to form a sulphone of formula (iii)



(i i i)

and thereafter either

(c) reacting the sulphone with lithium diisopropyl amide and then with dimethylcarbonate to form alpha and beta C-1 substituted sugars of formula (iv)



(i v)

and

(c') isolating the C-1 substituted sugar,

or

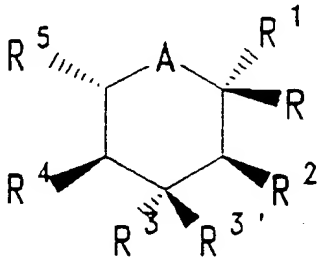
(d) reacting the sulphone with lithium diisopropyl amide in the presence of lithium naphthalenide and a compound containing a COOH, $P(O)(OH)_2$ or SOOH group

and

(d') isolating the desired compound of formula I.

34. A method according to Claim 33, wherein in step (e) the compound containing the $P(O)(OH)_2$ group is diethyl chlorophosphate.

35. A glycosyl halide of general formula III



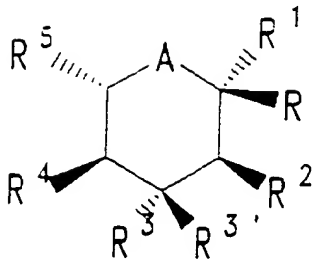
I I I

wherein R may be F, Cl or Br, when R^2 is not H, F, Cl or Br;

if R^3, $R^{3'}$ is OR^6 or H then R^4 is NH-acyl; and

A, R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and R^6 are as defined in Claim 25.

36. A method of synthesis of a compound of general formula I, as defined in Claim 25, which comprises the step of reacting a glycosyl halide of general formula III



III

wherein R may be F, Cl or Br when R^2 is not H, F, Cl or Br;

if R^3, $R^{3'}$ is OR^6 or H then R^4 is NH-acyl; and

A, R^1, R^2, R^3, $R^{3'}$, R^4, R^5 and R^6 are as defined in Claim 25, with a nucleophile which is a group which can be converted to a desired functional group R^1, and recovering said compound of general formula III.

37. An improved method of synthesis of glycosyl halides of general formula III as defined in Claim 35, comprising the step of treating the corresponding neuraminic acid analogue with excess acetyl halide at room temperature under a nitrogen atmosphere until no starting material is observable by thin layer chromatography, and recovering the desired glycosyl halide.

38. A compound according to Claim 18, synthesised using an intermediate compound selected from the group consisting of 2,3-didehydro-α-D-neuraminic acid; 3,4,6-tri-O-acetyl-2-deoxy-β-L-arabinohexepyranosyl thiophenoxide; 4-O-benzyl-3,6-bis(t-butylmethylsilyloxy)-2-deoxy-β-L-arabino-hexepyranosyl thiophenoxide; 4-O-benzyl-3,6-bis(t-butylmethylsilyloxy)-2-deoxy-β-L-arabinohexepyranosyl phenylsulphone; α-carboxy-methyl-β-phenylsulphonyl-4-O-benzyl-3,6-bis (t-butyldimethyl-silyloxy)-2-deoxy-L-arabinohexepyranose; methyl-4-O-benzyl-3,6-bis(t-butyldimethylsilyloxy)-2-deoxy-α-L-arabinohexepyranosyl-carboxylate, and methyl-N-acetyl-4,7,8,9-tetra-O-acetyl-2-β-chloro-2-β-deoxy-D-neuraminate.

FIGURE 1

TYR CB	84	84.15	84.36	34.64	: TYR CG	84	85.21	85.21	34.87
TYR CD1	84	85.98	82.90	33.81	: TYR CE1	84	86.93	86.93	33.99
TYR CD2	84	85.38	82.71	36.12	: TYR CE2	84	86.33	86.33	36.28
TYR CZ	84	87.09	81.36	35.22	: TYR OH	84	88.02	88.02	35.44
TYR C	84	82.21	85.61	35.47	: TYR O	84	81.78	81.78	34.45
TYR N	84	81.80	83.51	34.56	: TYR CA	84	82.81	82.81	35.35
ARG N	85	82.11	86.13	36.69	: ARG CA	85	81.55	81.55	36.96
ARG CB	85	81.28	87.60	38.45	: ARG CG	85	80.32	80.32	39.01
ARG CD	85	79.54	87.11	40.19	: ARG NE	85	80.16	80.16	41.45
ARG CZ	85	79.46	86.85	42.60	: ARG NH1	85	80.06	80.06	43.73
ARG NH2	85	78.16	87.08	42.68	: ARG C	85	82.60	82.60	36.53
ARG O	85	83.80	88.28	36.84	: ASN N	86	82.17	82.17	35.75
ASN CA	86	83.03	90.53	35.37	: ASN CB	86	83.09	83.09	33.87
ASN CG	86	81.77	91.10	33.23	: ASN OD1	86	80.88	80.88	33.85
ASN ND2	86	81.58	90.77	31.96	: ASN D22	86	82.34	82.34	31.48
ASN C	86	82.54	91.85	35.97	: ASN O	86	83.14	83.14	35.73
TRP N	87	81.43	91.88	36.71	: TRP CA	87	80.82	80.82	37.33
TRP CB	87	81.57	93.35	38.61	: TRP CG	87	81.56	81.56	39.62
TRP CD2	87	80.61	91.94	40.57	: TRP CE2	87	81.18	81.18	41.26
TRP CE3	87	79.39	92.41	40.99	: TRP CD1	87	82.64	82.64	39.70
TRP NE1	87	82.37	90.59	40.71	: TRP CZ2	87	80.57	80.57	42.34
TRP CZ3	87	78.76	91.83	42.07	: TRP CH2	87	79.35	79.35	42.74
TRP C	87	80.68	94.34	36.53	: TRP O	87	80.68	80.68	37.12
SER N	88	80.53	94.34	35.21	: SER CA	88	80.49	80.49	34.49
SER CB	88	81.04	95.33	33.11	: SER OG	88	80.50	80.50	32.49
SER C	88	79.08	96.14	34.45	: SER O	88	78.37	78.37	33.44
LYS N	89	78.62	96.69	35.55	: LYS CA	89	77.30	77.30	35.60
LYS CB	89	76.27	96.27	36.18	: LYS CG	89	75.43	75.43	35.10
LYS CD	89	74.50	94.62	35.78	: LYS CE	89	73.78	73.78	34.72
LYS NZ	89	73.32	92.56	35.32	: LYS C	89	77.40	77.40	36.51
LYS O	89	78.14	98.43	37.51	: PRO N	90	76.68	76.68	36.21
PRO CD	90	75.82	99.64	35.04	: PRO CA	90	76.66	76.66	36.98
PRO CB	90	75.57	101.54	36.34	: PRO CG	90	75.60	75.60	34.88
PRO C	90	76.39	100.42	38.40	: PRO O	90	75.68	75.68	38.67
GLN N	91	76.95	101.12	39.35	: GLN CA	91	76.51	76.51	40.72
GLN CB	91	77.43	101.77	41.62	: GLN CG	91	77.11	77.11	43.08
GLN CD	91	78.10	102.47	43.94	: GLN OE1	91	79.17	79.17	44.31
GLN NE2	91	77.86	103.70	44.35	: GLN E21	91	76.98	76.98	44.15
GLN E22	91	78.59	104.13	44.87	: GLN C	91	75.07	75.07	40.72
GLN O	91	74.65	102.43	39.95	: CYS N	92	74.24	74.24	41.53
CYS CA	92	72.89	101.43	41.68	: CYS C	92	72.97	72.97	42.48
CYS O	92	73.82	102.91	43.37	: CYS CB	92	72.03	72.03	42.47
CYS SG	92	71.93	98.76	41.94	: GLN N	93	72.08	72.08	42.09
GLN CA	93	71.92	104.93	42.79	: GLN CB	93	71.17	71.17	41.90
GLN CG	93	72.12	106.61	40.92	: GLN CD	93	73.20	73.20	41.61
GLN OE1	93	73.18	107.78	42.81	: GLN NE2	93	74.24	74.24	40.87
GLN E21	93	74.31	107.45	39.95	: GLN E22	93	74.89	74.89	41.25
GLN C	93	71.10	104.56	44.00	: GLN O	93	70.09	70.09	43.86
ILE N	94	71.59	104.86	45.17	: ILE CA	94	70.89	70.89	46.34
ILE CB	94	71.77	103.47	47.29	: ILE CG2	94	72.35	72.35	46.47
ILE CG1	94	72.90	104.19	47.95	: ILE CD1	94	73.31	73.31	49.25
ILE C	94	70.57	105.73	47.05	: ILE O	94	71.22	71.22	46.88
THR N	95	69.60	105.57	47.93	: THR CA	95	68.91	68.91	48.70
THR CB	95	67.42	106.37	48.37	: THR OG1	95	67.30	67.30	46.96
THR CG2	95	66.48	107.25	49.11	: THR C	95	69.24	69.24	50.16
THR O	95	68.93	107.22	50.99	: GLY N	96	69.78	69.78	50.50
GLY CA	96	70.06	104.81	51.87	: GLY C	96	69.94	69.94	51.93
GLY O	96	69.98	102.60	50.90	: PHE N	97	69.68	69.68	53.11

FIGURE 1 (cont.)

PHE	CA	97	69.74	101.31	53.38	: PHE	CB	97	70.94	70.94	54.35
PHE	CG	97	72.23	101.42	53.62	: PHE	CD1	97	72.60	72.60	52.49
PHE	CD2	97	72.98	102.54	54.00	: PHE	CE1	97	73.69	73.69	51.73
PHE	CE2	97	74.07	102.93	53.22	: PHE	CZ	97	74.43	74.43	52.10
PHE	C	97	68.47	100.74	53.95	: PHE	O	97	67.90	67.90	54.85
ALA	N	98	68.04	99.59	53.44	: ALA	CA	98	66.83	66.83	53.89
ALA	CB	98	66.04	98.47	52.69	: ALA	C	98	67.24	67.24	54.70
ALA	O	98	68.25	97.06	54.36	: PRO	N	99	66.57	66.57	55.77
PRO	CD	99	65.32	97.81	56.23	: PRO	CA	99	66.89	66.89	56.50
PRO	CB	99	65.83	95.92	57.58	: PRO	CG	99	65.32	65.32	57.69
PRO	C	99	66.98	94.72	55.63	: PRO	O	99	66.22	66.22	54.66
PHE	N	100	67.90	93.78	55.89	: PHE	CA	100	68.01	68.01	54.98
PHE	CB	100	69.23	92.82	54.11	: PHE	CG	100	69.38	69.38	52.97
PHE	CD1	100	70.60	91.19	52.78	: PHE	CD2	100	68.34	68.34	52 09
PHE	CE1	100	70.79	90.32	51.72	: PHE	CE2	100	68.56	68.56	51.03
PHE	CZ	100	69.78	90.08	50.83	: PHE	C	100	68.09	68.09	55.67
PHE	O	100	67.52	90.36	55.15	: SER	N	101	68.80	68.80	56.78
SER	CA	101	68.89	89.88	57.40	: SER	CB	101	69.90	69.90	56.67
SER	OG	101	69.78	87.70	57.10	: SER	C	101	69.36	69.36	58.79
SER	O	101	69.79	91.32	59.05	: LYS	N	102	69.13	69.13	59.67
LYS	CA	102	69.58	89.29	61.04	: LYS	CB	102	68.68	68.68	61.85
LYS	CG	102	68.94	90.20	63.32	: LYS	CD	102	68.45	68.45	63.88
LYS	CE	102	68.19	91.50	65.37	: LYS	NZ	102	69.34	69.34	66.16
LYS	C	102	69.46	87.82	61.44	: LYS	O	102	68.40	68.40	61.28
ASP	N	103	70.56	87.13	61.70	: ASP	CA	103	70.45	70.45	62.23
ASP	CB	103	71.73	84.97	61.94	: ASP	CG	103	73.08	73.08	62.56
ASP	OD1	103	73.15	86.19	63.51	: ASP	OD2	103	74.10	74.10	62.09
ASP	C	103	70.28	85.98	63.72	: ASP	O	103	70.67	70.67	64.10
ASN	N	104	69.89	85.20	64.72	: ASN	CA	104	69.85	69.85	66.05
ASN	CB	104	68.39	86.02	66.54	: ASN	CG	104	67.59	67.59	66.07
ASN	OD1	104	66.98	87.28	64.99	: ASN	ND2	104	67.49	67.49	66.85
ASN	D21	104	67.92	88.29	67.73	: ASN	D22	104	67.03	67.03	66.43
ASN	C	104	70.66	85.02	67.01	: ASN	O	104	70.25	70.25	68.15
SER	N	105	71.85	84.62	66.49	: SER	CA	105	72.80	72.80	67.13
SER	CB	105	74.09	83.41	66.22	: SER	OG	105	73.98	73.98	64.93
SER	C	105	73.29	84.35	68.40	: SER	O	105	74.25	74.25	68.24
ILE	N	106	72.67	84.26	69.57	: ILE	CA	106	73.14	73.14	70.88
ILE	CB	106	73.68	86.25	71.12	: ILE	CG2	106	74.13	74.13	72.58
ILE	CG1	106	75.01	86.69	70.46	: ILE	CD1	106	76.26	76.26	70.67
ILE	C	106	71.87	84.69	71.71	: ILE	O	106	71.87	71.87	72.76
ARG	N	107	70.75	85.29	71.26	: ARG	CA	107	69.47	69.47	72.00
ARG	CB	107	68.25	85.87	71.36	: ARG	CG	107	68.32	68.32	71.04
ARG	CD	107	66.98	87.88	70.53	: ARG	NE	107	66.21	66.21	71.68
ARG	CZ	107	64.89	88.28	71.77	: ARG	NH1	107	64.36	64.36	72.89
ARG	NH2	107	64.09	87.84	70.81	: ARG	C	107	69.15	69.15	71.97
ARG	O	107	68.93	83.12	73.04	: LEU	N	108	69.26	69.26	70.75
LEU	CA	108	69.15	81.70	70.46	: LEU	CB	108	69.38	69.38	68.97
LEU	CG	108	68.35	81.90	67.95	: LEU	CD1	108	68.84	68.84	66.56
LEU	CD2	108	67.02	81.18	68.18	: LEU	C	108	70.10	70.10	71.26
LEU	O	108	69.69	79.79	71.85	: SER	N	109	71.38	71.38	71.41
SER	CA	109	72.39	80.39	72.13	: SER	CB	109	73.72	73.72	72.03
SER	OG	109	73.91	81.68	70.72	: SER	C	109	72.03	72.03	73.57
SER	O	109	72.67	79.38	74.27	: ALA	N	110	71.01	71.01	74.08
ALA	CA	110	70.60	80.63	75.44	: ALA	CB	110	70.06	70.06	76.00
ALA	C	110	69.52	79.52	75.49	: ALA	O	110	68.89	68.89	76.53
GLY	N	111	69.28	78.86	74.36	: GLY	CA	111	68.31	68.31	74.26
GLY	C	111	68.53	77.12	72.93	: GLY	O	111	67.63	67.63	72.08
GLY	N	112	69.73	76.60	72.73	: GLY	CA	112	70.10	70.10	71.49

FIGURE 1 (cont.)

GLY C	112	71.61	75.75	71.42	: GLY O	112	72.32	72.32	72.21
ASP N	113	72.16	74.90	70.55	: ASP CA	113	73.61	73.61	70.48
ASP CB	113	73.94	73.20	70.40	: ASP CG	113	73.36	73.36	71.55
ASP OD1	113	72.65	71.41	71.29	: ASP OD2	113	73.59	73.59	72.72
ASP C	113	74.04	75.43	69.22	: ASP O	113	73.81	73.81	68.09
ILE N	114	74.51	76.66	69.49	: ILE CA	114	74.99	74.99	68.49
ILE CB	114	74.16	78.97	68.65	: ILE CG2	114	74.62	74.62	67.57
ILE CG1	114	72.65	78.75	68.51	: ILE CD1	114	72.14	72.14	67.11
ILE C	114	76.48	77.92	68.70	: ILE O	114	76.97	76.97	69.83
TRP N	115	77.24	77.91	67.62	: TRP CA	115	78.66	78.66	67.61
TRP CB	115	79.20	78.22	66.21	: TRP CG	115	79.43	79.43	65.63
TRP CD2	115	80.66	76.24	65.60	: TRP CE2	115	80.41	80.41	64.88
TRP CE3	115	81.91	76.60	66.08	: TRP CD1	115	78.46	78.46	65.01
TRP NE1	115	79.09	75.03	64.56	: TRP CZ2	115	81.48	81.48	64.64
TRP CZ3	115	82.95	75.73	65.82	: TRP CH2	115	82.74	82.74	65.11
TRP C	115	79.07	79.53	68.20	: TRP O	115	78.37	78.37	68.06
VAL N	116	80.23	79.56	68.86	: VAL CA	116	80.85	80.85	69.31
VAL CB	116	81.86	80.58	70.42	: VAL CG1	116	82.62	82.62	70.70
VAL CG2	116	81.13	80.24	71.71	: VAL C	116	81.59	81.59	68.10
VAL O	116	82.28	80.55	67.46	: THR N	117	81.41	81.41	67.67
THR CA	117	82.11	83.07	66.49	: THR CB	117	81.18	81.18	65.19
THR OG1	117	79.96	83.76	65.41	: THR CG2	117	80.87	80.87	64.76
THR C	117	82.65	84.49	66.72	: THR O	117	82.54	82.54	67.83
ARG N	118	83.36	85.04	65.72	: ARG CA	118	83.67	83.67	65.61
ARG CB	118	84.73	86.94	66.61	: ARG CG	118	84.02	84.02	67.50
ARG CD	118	84.76	88.98	68.47	: ARG NE	118	85.90	85.90	67.90
ARG CZ	118	85.81	90.64	66.96	: ARG NH1	118	86.86	86.86	66.38
ARG NH2	118	84.67	91.12	66.58	: ARG C	118	84.16	84.16	64.17
ARG O	118	84.26	85.68	63.37	: GLU N	119	84.43	84.43	63.81
GLU CA	119	84.80	88.31	62.47	: GLU CB	119	86.27	86.27	62.12
GLU CG	119	87.31	88.53	63.11	: GLU CD	119	87.40	87.40	64.36
GLU OE1	119	87.27	86.47	64.24	: GLU OE2	119	87.59	87.59	65.47
GLU C	119	83.91	87.69	61.41	: GLU O	119	84.40	84.40	60.53
PRO N	120	82.57	87.96	61.44	: PRO CD	120	81.86	81.86	62.43
PRO CA	120	81.60	87.53	60.44	: PRO CB	120	80.27	80.27	61.11
PRO CG	120	80.45	88.96	61.87	: PRO C	120	81.63	81.63	59.16
PRO O	120	82.10	89.45	59.18	: TYR N	121	81.17	81.17	58.04
TYR CA	121	81.11	88.65	56.85	: TYR CB	121	82.46	82.46	56.17
TYR CG	121	83.29	87.48	55.75	: TYR CD1	121	83.19	83.19	54.46
TYR CE1	121	83.97	86.00	54.05	: TYR CD2	121	84.12	84.12	56.66
TYR CE2	121	84.89	85.82	56.27	: TYR CZ	121	84.78	84.78	54.97
TYR OH	121	85.51	84.33	54.53	: TYR C	121	80.09	80.09	55.97
TYR O	121	79.69	86.87	56.31	: VAL N	122	79.53	79.53	54.90
VAL CA	122	78.66	87.71	54.12	: VAL CB	122	77.07	77.07	54.30
VAL CG1	122	76.84	88.73	55.62	: VAL CG2	122	76.48	76.48	53.12
VAL C	122	79.13	87.91	52.71	: VAL O	122	79.78	79.78	52.36
SER N	123	78.98	86.89	51.90	: SER CA	123	79.38	79.38	50.51
SER CB	123	80.78	86.43	50.17	: SER OG	123	81.03	81.03	48.76
SER C	123	78.30	86.24	49.85	: SER O	123	77.58	77.58	50.45
CYS N	124	78.25	86.37	48.54	: CYS CA	124	77.01	77.01	47.90
CYS C	124	77.32	85.56	46.51	: CYS O	124	78.01	78.01	45.69
CYS CB	124	76.43	87.50	48.14	: CYS SG	124	74.70	74.70	47.89
ASP N	125	76.93	84.32	46.22	: ASP CA	125	77.25	77.25	44.92
ASP CB	125	77.25	82.22	45.03	: ASP CG	125	75.88	75.88	44.91
ASP OD1	125	75.23	81.36	45.92	: ASP OD2	125	75.46	75.46	43.81
ASP C	125	76.25	84.22	43.90	: ASP O	125	75.28	75.28	44.33
PRO N	126	76.29	83.97	42.60	: PRO CD	126	77.36	77.36	41.87
PRO CA	126	75.30	84.53	41.69	: PRO CB	126	75.84	75.84	40.29

PRO	CG	126	76.75	83.06	40.50	: PRO	C	126	73.86	73.86	41.86
PRO	O	126	73.04	84.55	41.06	: VAL	N	127	73.46	73.46	42.80
VAL	CA	127	72.04	82.92	43.05	: VAL	CB	127	71.58	71.58	42.87
VAL	CG1	127	72.00	81.00	41.49	: VAL	CG2	127	72.17	72.17	43.88
VAL	C	127	71.70	83.30	44.48	: VAL	O	127	70.69	70.69	44.69
LYS	N	128	72.52	82.99	45.50	: LYS	CA	128	72.14	72.14	46.85
LYS	CB	128	71.49	82.10	47.52	: LYS	CG	128	72.29	72.29	47.49
LYS	CD	128	71.71	79.79	48.44	: LYS	CE	128	70.77	70.77	47.72
LYS	NZ	128	70.32	77.88	48.75	: LYS	C	128	73.27	73.27	47.72
LYS	O	128	74.40	83.83	47.29	: CYS	N	129	73.01	73.01	48.96
CYS	CA	129	73.99	84.79	49.82	: CYS	C	129	74.25	74.25	51.01
CYS	O	129	73.30	83.39	51.62	: CYS	CB	129	73.57	73.57	50.47
CYS	SG	129	73.61	87.66	49.57	: TYR	N	130	75.51	75.51	51.44
TYR	CA	130	75.96	83.14	52.55	: TYR	CB	130	76.99	76.99	52.09
TYR	CG	130	76.43	81.21	51.03	: TYR	CD1	130	75.89	75.89	51.39
TYR	CE1	130	75.34	79.14	50.45	: TYR	CD2	130	76.42	76.42	49.71
TYR	CE2	130	75.87	80.79	48.77	: TYR	CZ	130	75.34	75.34	49.14
TYR	OH	130	74.86	78.71	48.15	: TYR	C	130	76.56	76.56	53.61
TYR	O	130	77.17	85.06	53.33	: GLN	N	131	76.40	76.40	54.84
GLN	CA	131	77.04	84.32	55.91	: GLN	CB	131	76.03	76.03	57.02
GLN	CG	131	75.38	83.28	57.63	: GLN	CD	131	74.54	74.54	58.81
GLN	OE1	131	74.83	83.35	59.94	: GLN	NE2	131	73.48	73.48	58.66
GLN	E21	131	73.28	84.91	57.79	: GLN	E22	131	72.96	72.96	59.47
GLN	C	131	78.21	83.40	56.34	: GLN	O	131	78.08	78.08	56.47
PHE	N	132	79.39	84.01	56.59	: PHE	CA	132	80.58	80.58	57.03
PHE	CB	132	81.69	83.59	56.12	: PHE	CG	132	81.42	81.42	54.68
PHE	CD1	132	81.99	82.12	54.15	: PHE	CD2	132	80.63	80.63	53.92
PHE	CE1	132	81.80	81.81	52.83	: PHE	CE2	132	80.44	80.44	52.59
PHE	CZ	132	81.02	82.62	52.05	: PHE	C	132	81.01	81.01	58.39
PHE	O	132	80.68	84.92	58.79	: ALA	N	133	81.73	81.73	59.19
ALA	CA	133	82.25	83.59	60.46	: ALA	CB	133	81.24	81.24	61.58
ALA	C	133	83.39	82.68	60.91	: ALA	O	133	83.51	83.51	60.44
LEU	N	134	84.22	83.16	61.82	: LEU	CA	134	85.38	85.38	62.23
LEU	CB	134	86.49	83.43	62.44	: LEU	CG	134	87.75	87.75	61.64
LEU	CD1	134	87.48	82.85	60.22	: LEU	CD2	134	88.40	88.40	61 58
LEU	C	134	84.88	81.80	63.49	: LEU	O	134	84.57	84.57	64.43
GLY	N	135	84.70	80.46	63.52	: GLY	CA	135	84.20	84.20	64.71
GLY	C	135	85.26	79.67	65.79	: GLY	O	135	86.42	86.42	65.44
GLN	N	136	84.99	79.48	67.07	: GLN	CA	136	86.05	86.05	68.02
GLN	CB	136	85.76	80.06	69.27	: GLN	CG	136	85.96	85.96	69.10
GLN	CD	136	87.41	82.02	69.03	: GLN	OE1	136	88.35	88.35	69.21
GLN	NE2	136	87.66	83.29	68.76	: GLN	E21	136	86.91	86.91	68.61
GLN	E22	136	88.59	83.57	68.66	: GLN	C	136	86.09	86.09	68.34
GLN	O	136	86.33	77.36	69.49	: GLY	N	137	85.85	85.85	67.39
GLY	CA	137	85.81	75.38	67.67	: GLY	C	137	84.90	84.90	68.82
GLY	O	137	85.17	73.90	69.44	: THR	N	138	83.81	83.81	69.12
THR	CA	138	82.99	75.35	70.29	: THR	CB	138	83.76	83.76	71.55
THR	OG1	138	83.08	75.37	72.69	: THR	CG2	138	83.82	83.82	71.65
THR	C	138	81.64	76.06	70.08	: THR	O	138	81.45	81.45	69.15
THR	N	139	80.70	75.67	70.95	: THR	CA	139	79.36	79.36	71.01
THR	CB	139	78.25	75.15	71.07	: THR	OG1	139	78.57	78.57	72.10
THR	CG2	139	78.01	74.57	69.69	: THR	C	139	79.34	79.34	72.29
THR	O	139	80.27	77.00	73.11	: LEU	N	140	78.33	78.33	72.50
LEU	CA	140	78.37	78.84	73.62	: LEU	CB	140	77.43	77.43	73.28
LEU	CG	140	77.53	81.29	74.01	: LEU	CD1	140	77.17	77.17	73.04
LEU	CD2	140	76.65	81.27	75.23	: LEU	C	140	78.05	78.05	74.93
LEU	O	140	78.67	78.50	75.95	: ASP	N	141	77.08	77.08	74.99
ASP	CA	141	76.81	76.57	76.23	: ASP	CB	141	75.33	75.33	76.33

FIGURE 1 (cont.)

ASP	CG	141	74.84	76.01	77.75	ASP	OD1	141	75.61	75.61	78.70
ASP	OD2	141	73.63	75.96	77.90	ASP	C	141	77.65	77.65	76.11
ASP	O	141	77.24	74.24	75.62	ASN	N	142	78.91	78.91	76.49
ASN	CA	142	79.95	74.51	76.35	ASN	CB	142	80.36	80.36	74.88
ASN	CG	142	81.20	73.32	74.44	ASN	OD1	142	81.06	81.06	73.37
ASN	ND2	142	82.13	72.80	75.21	ASN	D21	142	82.34	82.34	76.08
ASN	D22	142	82.45	71.95	74.83	ASN	C	142	81.06	81.06	77.25
ASN	O	142	81.46	76.18	77.04	LYS	N	143	81.69	81.69	78.24
LYS	CA	143	82.72	73.01	79.07	LYS	CB	143	83.21	83.21	80.15
LYS	CG	143	82.17	73.46	81.10	LYS	CD	143	82.84	82.84	82.43
LYS	CE	143	82.18	72.08	83.36	LYS	NZ	143	82.77	82.77	83.18
LYS	C	143	83.93	75.53	78.29	LYS	O	143	84.70	84.70	78.74
HIS	N	144	84.07	75.06	77.04	HIS	CA	144	85.16	85.16	76.14
HIS	CB	144	85.32	74.46	74.92	HIS	CG	144	85.66	85.66	75.20
HIS	CD2	144	86.76	72.57	75.88	HIS	ND1	144	84.94	84.94	74.90
HIS	CE1	144	85.55	70.87	75.39	HIS	NE2	144	86.64	86.64	75.99
HIS	C	144	84.92	76.79	75.54	HIS	O	144	85.72	85.72	74.70
SER	N	145	83.82	77.50	75.81	SER	CA	145	83.64	83.64	75.30
SER	CB	145	82.16	79.13	75.30	SER	OG	145	81.61	81.61	76.58
SER	C	145	84.40	79.83	76.18	SER	O	145	84.65	84.65	75.79
ASN	N	146	84.76	79.41	77.40	ASN	CA	146	85.51	85.51	78.35
ASN	CB	146	85.74	79.44	79.63	ASN	CG	146	86.38	86.38	80.74
ASN	OD1	146	86.80	81.42	80.56	ASN	ND2	146	86.42	86.42	81.93
ASN	D22	146	86.25	78.71	81.96	ASN	C	146	86.85	86.85	77.82
ASN	O	146	87.70	79.82	77.53	ASP	N	147	86.99	86.99	77.73
ASP	CA	147	88.15	82.72	77.24	ASP	CB	147	89.42	89.42	77.88
ASP	CG	147	90.64	83.03	78.12	ASP	OD1	147	91.65	91.65	78.52
ASP	OD2	147	90.64	84.25	77.90	ASP	C	147	88.29	88.29	75.73
ASP	O	147	89.39	82.79	75.16	THR	N	148	87.17	87.17	75.02
THR	CA	148	87.23	82.88	73.57	THR	CB	148	85.90	85.90	73.00
THR	OG1	148	84.82	82.85	73.77	THR	CG2	148	85.94	85.94	72.96
THR	C	148	87.50	84.30	73.06	THR	O	148	87.20	87.20	71.89
VAL	N	149	87.95	85.23	73.93	VAL	CA	149	88.37	88.37	73.50
VAL	CB	149	88.94	87.53	74.58	VAL	CG1	149	88.07	88.07	74.54
VAL	CG2	149	88.99	86.94	75.97	VAL	C	149	89.54	89.54	72.53
VAL	O	149	89.68	87.25	71.61	HIS	N	150	90.41	90.41	72.74
HIS	CA	150	91.61	85.30	71.93	HIS	CB	150	92.43	92.43	72.40
HIS	CG	150	92.72	84.28	73.88	HIS	CD2	150	92.33	92.33	74.75
HIS	ND1	150	93.29	85.25	74.60	HIS	CE1	150	93.26	93.26	75.87
HIS	NE2	150	92.68	83.72	75.93	HIS	C	150	91.29	91.29	70.48
HIS	O	150	90.50	84.22	70.08	ASP	N	151	91.96	91.96	69.70
ASP	CA	151	91.70	85.84	68.29	ASP	CB	151	92.28	92.28	67.60
ASP	CG	151	91.87	88.46	68.15	ASP	OD1	151	91.80	91.80	69.37
ASP	OD2	151	91.66	89.37	67.33	ASP	C	151	92.29	92.29	67.62
ASP	O	151	91.83	84.31	66.53	ARG	N	152	93.31	93.31	68.16
ARG	CA	152	93.94	82.93	67.36	ARG	CB	152	95.26	95.26	66.82
ARG	CG	152	95.19	84.52	65.75	ARG	CD	152	96.57	96.57	65.41
ARG	NE	152	96.78	86.43	66.01	ARG	CZ	152	97.41	97.41	67.16
ARG	NH1	152	97.53	87.85	67.62	ARG	NH2	152	97.94	97.94	67.90
ARG	C	152	94.17	81.64	68.10	ARG	O	152	94.84	94.84	69.12
ILE	N	153	93.55	80.51	67.71	ILE	CA	153	93.77	93.77	68.34
ILE	CB	153	92.66	78.81	69.37	ILE	CG2	153	92.89	92.89	70.63
ILE	CG1	153	91.25	79.00	68.83	ILE	CD1	153	90.19	90.19	69.74
ILE	C	153	93.76	78.20	67.20	ILE	O	153	93.20	93.20	66.14
PRO	N	154	94.35	76.98	67.24	PRO	CD	154	94.92	94.92	68.42
PRO	CA	154	94.33	76.05	66.10	PRO	CB	154	95.26	95.26	66.52
PRO	CG	154	95.93	75.40	67.78	PRO	C	154	92.91	92.91	65.72
PRO	O	154	92.64	74.92	64.70	HIS	N	155	91.95	91.95	66.59

FIGURE 1 (cont.)

HIS	CA	155	90.60	75.32	66.48	: HIS	CB	155	90.15	90.15	67.88
HIS	CG	155	91.18	74.14	68.55	: HIS	CD2	155	91.52	91.52	69.87
HIS	ND1	155	91.95	73.19	68.01	: HIS	CE1	155	92.71	92.71	68.92
HIS	NE2	155	92.43	73.29	70.02	: HIS	C	155	89.61	89.61	65.77
HIS	O	155	88.43	75.90	65.78	: ARG	N	156	90.04	90.04	65.15
ARG	CA	156	89.12	78.27	64.53	: ARG	CB	156	89.64	89.64	64.53
ARG	CG	156	90.03	80.17	65.92	: ARG	CD	156	89.90	89.90	66.12
ARG	NE	156	88.50	82.05	66.04	: ARG	CZ	156	88.09	88.09	65.80
ARG	NH1	156	86.79	83.57	65.74	: ARG	NH2	156	88.95	88.95	65.68
ARG	C	156	89.07	77.74	63.10	: ARG	O	156	90.09	90.09	62.50
THR	N	157	87.84	77.76	62.59	: THR	CA	157	87.48	87.48	61.28
THR	CB	157	86.80	75.86	61.51	: THR	OG1	157	85.94	85.94	62.65
THR	CG2	157	87.75	74.69	61.75	: THR	C	157	86.53	86.53	60.62
THR	O	157	85.74	78.89	61.30	: LEU	N	158	86.53	86.53	59.31
LEU	CA	158	85.60	79.28	58.65	: LEU	CB	158	86.14	86.14	57.26
LEU	CG	158	85.27	80.39	56.26	: LEU	CD1	158	84.98	84.98	56.85
LEU	CD2	158	85.94	80.51	54.88	: LEU	C	158	84.23	84.23	58.55
LEU	O	158	84.13	77.56	57.85	: LEU	N	159	83.18	83.18	59.24
LEU	CA	159	81.85	78.47	59.10	: LEU	CB	159	81.07	81.07	60.31
LEU	CG	159	81.71	78.36	61.58	: LEU	CD1	159	80.92	80.92	62.78
LEU	CD2	159	81.83	76.85	61.51	: LEU	C	159	81.18	81.18	57.86
LEU	O	159	81.49	80.21	57.56	: MET	N	160	80.34	80.34	57.08
MET	CA	160	79.63	78.99	55.95	: MET	CB	160	80.27	80.27	54.65
MET	CG	160	79.53	79.07	53.42	: MET	SD	160	80.47	80.47	51.99
MET	CE	160	79.66	78.88	50.47	: MET	C	160	78.16	78.16	55.95
MET	O	160	77.91	77.27	55.88	: ASN	N	161	77.14	77.14	55.97
ASN	CA	161	75.74	78.98	56.00	: ASN	CB	161	75.11	75.11	57.34
ASN	CG	161	75.03	77.92	58.15	: ASN	OD1	161	74.99	74.99	59.38
ASN	ND2	161	74.95	76.74	57.56	: ASN	D21	161	74.88	74.88	56.59
ASN	D22	161	74.96	75.97	58.15	: ASN	C	161	75.00	75.00	55.05
ASN	O	161	75.57	80.83	54.54	: GLU	N	162	73.75	73.75	54.69
GLU	CA	162	72.96	80.54	53.96	: GLU	CB	162	71.65	71.65	53.48
GLU	CG	162	71.75	79.01	52.38	: GLU	CD	162	70.39	70.39	51.75
GLU	OE1	162	69.98	77.60	51.72	: GLU	OE2	162	69.74	69.74	51.23
GLU	C	162	72.65	81.65	54.96	: GLU	O	162	72.49	72.49	56.19
LEU	N	163	72.61	82.86	54.39	: LEU	CA	163	72.27	72.27	55.12
LEU	CB	163	72.26	85.25	54.14	: LEU	CG	163	72.03	72.03	54.70
LEU	CD1	163	73.02	86.97	55.83	: LEU	CD2	163	72.12	72.12	53.55
LEU	C	163	70.88	83.83	55.74	: LEU	O	163	69.89	69.89	55.09
GLY	N	164	70.97	83.89	57.04	: GLY	CA	164	69.78	69.78	57.79
GLY	C	164	69.72	82.50	58.55	: GLY	O	164	69.12	69.12	59.65
VAL	N	165	70.33	81.41	58.06	: VAL	CA	165	70.32	70.32	58.95
VAL	CB	165	70.28	78.85	58.10	: VAL	CG1	165	70.22	70.22	56.60
VAL	CG2	165	71.39	77.94	58.53	: VAL	C	165	71.53	71.53	59.89
VAL	O	165	72.65	80.69	59.47	: PRO	N	166	71.33	71.33	61.21
PRO	CD	166	70.02	80.18	61.83	: PRO	CA	166	72.39	72.39	62.18
PRO	CB	166	71.61	80.87	63.44	: PRO	CG	166	70.37	70.37	63.30
PRO	C	166	73.39	79.42	62.28	: PRO	O	166	73.13	73.13	61.82
PHE	N	167	74.51	79.62	62.99	: PHE	CA	167	75.58	75.58	63.00
PHE	CB	167	76.93	79.35	63.24	: PHE	CG	167	77.27	77.27	62.12
PHE	CD1	167	77.31	79.90	60.80	: PHE	CD2	167	77.54	77.54	62.44
PHE	CE1	167	77.61	80.79	59.78	: PHE	CE2	167	77.84	77.84	61.41
PHE	CZ	167	77.88	82.10	60.10	: PHE	C	167	75.32	75.32	64.04
PHE	O	167	75.74	77.66	65.18	: HIS	N	168	74.48	74.48	63.59
HIS	CA	168	74.02	75.56	64.44	: HIS	CB	168	72.54	72.54	64.07
HIS	CG	168	72.40	74.78	62.65	: HIS	CD2	168	72.07	72.07	61.60
HIS	ND1	168	72.67	73.58	62.17	: HIS	CE1	168	72.52	72.52	60.86
HIS	NE2	168	72.16	74.83	60.51	: HIS	C	168	74.97	74.97	64.23

FIGURE 1 (cont.)

HIS O	168	75.89	74.50	63.41	: LEU N	169	74.76	74.76	64.86
LEU CA	169	75.71	72.06	64.75	: LEU CB	169	75.46	75.46	65.83
LEU CG	169	75.82	71.31	67.28	: LEU CD1	169	75.36	75.36	68.14
LEU CD2	169	77.31	71.51	67.42	: LEU C	169	75.80	75.80	63.45
LEU O	169	76.63	70.41	63.29	: GLY N	170	75.00	75.00	62.47
GLY CA	170	75.06	71.00	61.20	: GLY C	170	75.76	75.76	60.21
GLY O	170	75.66	71.73	58.98	: THR N	171	76.43	76.43	60.76
THR CA	171	77.11	73.95	59.96	: THR CB	171	77.32	77.32	60.78
THR OG1	171	76.01	75.64	61.14	: THR CG2	171	78.09	78.09	60.04
THR C	171	78.45	73.42	59.51	: THR O	171	79.20	79.20	60.24
ARG N	172	78.75	73.64	58.27	: ARG CA	172	80.02	80.02	57.72
ARG CB	172	79.85	73.26	56.27	: ARG CG	172	80.98	80.98	55.60
ARG CD	172	80.51	72.64	54.21	: ARG NE	172	81.61	81.61	53.68
ARG CZ	172	82.39	72.43	52.72	: ARG NH1	172	83.48	83.48	52.41
ARG NH2	172	82.05	73.58	52.07	: ARG C	172	81.19	81.19	58.13
ARG O	172	81.15	75.30	57.97	: GLN N	173	82.26	82.26	58.64
GLN CA	173	83.55	74.12	58.86	: GLN CB	173	84.27	84.27	59.96
GLN CG	173	83.33	73.44	61.13	: GLN CD	173	83.89	83.89	62.32
GLN OE1	173	84.74	73.25	62.99	: GLN NE2	173	83.49	83.49	62.76
GLN E21	173	82.79	71.07	62.29	: GLN E22	173	83.98	83.98	63.56
GLN C	173	84.30	73.96	57.54	: GLN O	173	84.82	84.82	57.25
VAL N	174	84.36	75.00	56.73	: VAL CA	174	84.99	84.99	55.42
VAL CB	174	84.46	76.33	54.74	: VAL CG1	174	85.10	85.10	53.40
VAL CG2	174	83.02	76.10	54.42	: VAL C	174	86.54	86.54	55.38
VAL O	174	87.10	74.61	54.32	: CYS N	175	87.27	87.27	56.44
CYS CA	175	88.72	75.21	56.45	: CYS C	175	89.18	89.18	57.81
CYS O	175	88.38	76.15	58.63	: CYS CB	175	89.33	89.33	55.45
CYS SG	175	88.90	77.89	55.74	: ILE N	176	90.49	90.49	58.06
ILE CA	176	91.07	75.90	59.33	: ILE CB	176	92.31	92.31	59.73
ILE CG2	176	92.49	75.19	61.24	: ILE CG1	176	92.10	92.10	59.41
ILE CD1	176	93.18	72.55	59.95	: ILE C	176	91.50	91.50	59.02
ILE O	176	92.14	77.62	57.99	: ALA N	177	91.09	91.09	59.83
ALA CA	177	91.35	79.71	59.53	: ALA CB	177	90.42	90.42	58.46
ALA C	177	91.09	80.50	60.79	: ALA O	177	90.07	90.07	61.45
TRP N	178	92.05	81.32	61.22	: TRP CA	178	91.79	91.79	62.24
TRP CB	178	92.82	82.24	63.42	: TRP CG	178	94.35	94.35	63.21
TRP CD2	178	95.21	82.93	62.51	: TRP CE2	178	96.43	96.43	62.76
TRP CE3	178	95.20	84.08	61.74	: TRP CD1	178	94.98	94.98	63.82
TRP NE1	178	96.24	81.23	63.51	: TRP CZ2	178	97.63	97.63	62.25
TRP CZ3	178	96.39	84.55	61.23	: TRP CH2	178	97.60	97.60	61.47
TRP C	178	91.81	83.68	61.56	: TRP O	178	91.75	91.75	62.23
SER N	179	91.89	83.74	60.22	: SER CA	179	91.68	91.68	59.45
SER CB	179	92.99	85.72	59.37	: SER OG	179	92.93	92.93	58.45
SER C	179	91.24	84.42	58.08	: SER O	179	91.74	91.74	57.73
SER N	180	90.40	85.09	57.25	: SER CA	180	89.85	89.85	55.99
SER CB	180	88.69	83.68	56.23	: SER OG	180	87.47	87.47	56.65
SER C	180	89.32	85.70	55.03	: SER O	180	89.21	89.21	55.37
SER N	181	88.93	85.24	53.85	: SER CA	181	88.24	88.24	52.86
SER CB	181	89.17	86.96	52.10	: SER OG	181	88.58	88.58	50.90
SER C	181	87.68	85.00	51.90	: SER O	181	88.37	88.37	51.58
SER N	182	86.44	85.13	51.41	: SER CA	182	85.87	85.87	50.46
SER CB	182	84.87	83.35	51.20	: SER OG	182	85.53	85.53	52.29
SER C	182	85.24	84.93	49.33	: SER O	182	84.89	84.89	49.53
CYS N	183	85.13	84.39	48.15	: CYS CA	183	84.49	84.49	47.08
CYS C	183	84.21	84.13	46.02	: CYS O	183	84.79	84.79	45.99
CYS CB	183	85.35	86.25	46.44	: CYS SG	183	87.08	87.08	45.92
HIS N	184	83.39	84.49	45.06	: HIS CA	184	82.97	82.97	44.11
HIS CB	184	81.51	83.24	44.53	: HIS CG	184	80.85	80.85	43.64

FIGURE 1 (cont.)

HIS	CD2	184	80.64	82.36	42.30	: HIS	ND1	184	80.44	80.44	43.99
HIS	CE1	184	79.99	80.39	42.90	: HIS	NE2	184	80.13	80.13	41.90
HIS	C	184	83.17	84.14	42.76	: HIS	O	184	82.52	82.52	42.42
ASP	N	185	83.99	83.58	41.90	: ASP	CA	185	84.26	84.26	40.57
ASP	CB	185	85.53	83.49	40.02	: ASP	CG	185	85.45	85.45	39.82
ASP	OD1	185	86.23	81.42	39.06	: ASP	OD2	185	84.62	84.62	40.44
ASP	C	185	83.23	84.02	39.48	: ASP	O	185	83.44	83.44	38.28
GLY	N	186	82.19	83.36	39.88	: GLY	CA	186	81.15	81.15	38.94
GLY	C	186	81.09	81.59	38.83	: GLY	O	186	80.04	80.04	39.16
LYS	N	187	82.19	80.90	38.51	: LYS	CA	187	82.19	82.19	38.42
LYS	CB	187	83.36	79.00	37.65	: LYS	CG	187	83.51	83.51	36.21
LYS	CD	187	84.60	78.55	35.54	: LYS	CE	187	85.61	85.61	36.46
LYS	NZ	187	86.68	78.46	37.11	: LYS	C	187	82.21	82.21	39.77
LYS	O	187	81.50	77.74	39.87	: ALA	N	188	82.97	82.97	40.82
ALA	CA	188	82.96	78.43	42.14	: ALA	CB	188	83.83	83.83	42.17
ALA	C	188	83.50	79.36	43.23	: ALA	O	188	83.78	83.78	42.95
TRP	N	189	83.53	78.93	44.49	: TRP	CA	189	84.00	84.00	45.63
TRP	CB	189	83.36	79.25	46.95	: TRP	CG	189	81.91	81.91	47.16
TRP	CD2	189	81.51	80.86	47.72	: TRP	CE2	189	80.14	80.14	47.54
TRP	CE3	189	82.11	81.95	48.32	: TRP	CD1	189	80.86	80.86	46.72
TRP	NE1	189	79.79	79.64	46.96	: TRP	CZ2	189	79.36	79.36	47.97
TRP	CZ3	189	81.32	83.01	48.74	: TRP	CH2	189	79.96	79.96	48.57
TRP	C	189	85.51	79.51	45.85	: TRP	O	189	86.03	86.03	45.58
LEU	N	190	86.22	80.56	46.27	: LEU	CA	190	87.62	87.62	46.69
LEU	CB	190	88.42	81.67	45.99	: LEU	CG	190	89.81	89.81	46.60
LEU	CD1	190	90.75	80.89	46.37	: LEU	CD2	190	90.35	90.35	46.00
LEU	C	190	87.55	80.85	48.16	: LEU	O	190	86.73	86.73	48.52
HIS	N	191	88.31	80.24	49.06	: HIS	CA	191	88.35	88.35	50.44
HIS	CB	191	87.72	79.64	51.37	: HIS	CG	191	86.28	86.28	51.02
HIS	CD2	191	85.98	78.20	50.25	: HIS	ND1	191	85.12	85.12	51.29
HIS	CE1	191	84.15	79.23	50.72	: HIS	NE2	191	84.69	84.69	50.10
HIS	C	191	89.85	80.79	50.73	: HIS	O	191	90.61	90.61	50.19
VAL	N	192	90.33	81.85	51.42	: VAL	CA	192	91.74	91.74	51.75
VAL	CB	192	92.43	83.28	51.22	: VAL	CG1	192	91.87	91.87	49.83
VAL	CG2	192	92.28	84.42	52.16	: VAL	C	192	91.63	91.63	53.24
VAL	O	192	90.90	82.64	53.89	: CYS	N	193	92.24	92.24	53.78
CYS	CA	193	92.07	80.52	55.17	: CYS	C	193	93.48	93.48	55.67
CYS	O	193	94.40	80.13	54.94	: CYS	CB	193	91.49	91.49	55.26
CYS	SG	193	89.96	78.81	54.29	: ILE	N	194	93.70	93.70	56.85
ILE	CA	194	95.02	81.33	57.41	: ILE	CB	194	95.31	95.31	57.44
ILE	CG2	194	96.63	83.18	58.12	: ILE	CG1	194	95.38	95.38	56.03
ILE	CD1	194	95.50	85.00	56.02	: ILE	C	194	95.11	95.11	58.80
ILE	O	194	94.30	81.04	59.67	: THR	N	195	95.96	95.96	59.09
THR	CA	195	96.13	79.26	60.47	: THR	CB	195	95.61	95.61	60.81
THR	OG1	195	95.32	77.24	59.55	: THR	CG2	195	94.57	94.57	61.92
THR	C	195	97.63	79.12	60.66	: THR	O	195	98.43	98.43	59.74
GLY	N	196	97.96	78.77	61.88	: GLY	CA	196	99.30	99.30	62.15
GLY	C	196	99.81	79.28	63.22	: GLY	O	196	99.11	99.11	63.99
ASP	N	197	101.12	79.19	63.25	: ASP	CA	197	101.82	101.82	64.21
ASP	CB	197	103.24	79.39	64.27	: ASP	CG	197	103.39	103.39	65.24
ASP	OD1	197	104.47	77.67	65.32	: ASP	OD2	197	102.47	102.47	66.00
ASP	C	197	101.79	81.45	63.82	: ASP	O	197	101.83	101.83	62.63
ASP	N	198	101.82	82.35	64.82	: ASP	CA	198	101.85	101.85	64.56
ASP	CB	198	101.93	84.58	65.86	: ASP	CG	198	100.67	100.67	66.72
ASP	OD1	198	99.59	84.28	66.20	: ASP	OD2	198	100.75	100.75	67.91
ASP	C	198	103.04	84.16	63.72	: ASP	O	198	102.92	102.92	62.60
LYS	N	199	104.18	83.73	64.27	: LYS	CA	199	105.45	105.45	63.67
LYS	CB	199	106.53	83.80	64.70	: LYS	CG	199	106.32	106.32	66.04

FIGURE 1 (cont.)

LYS	CD	199	106.36	86.11	66.02	LYS	CE	199	107.79	107.79	65.96
LYS	NZ	199	107.84	87.99	65.34	LYS	C	199	105.67	105.67	62.43
LYS	O	199	106.57	83.50	61.67	ASN	N	200	104.86	104.86	62.13
ASN	CA	200	105.08	81.36	60.91	ASN	CB	200	106.14	106.14	61.24
ASN	CG	200	106.87	79.75	60.03	ASN	OD1	200	106.75	106.75	58.87
ASN	ND2	200	107.67	78.73	60.36	ASN	D22	200	107.67	107.67	61.29
ASN	C	200	103.79	80.73	60.31	ASN	O	200	103.67	103.67	59.97
ALA	N	201	102.75	81.56	60.19	ALA	CA	201	101.48	101.48	59.64
ALA	CB	201	100.52	82.30	59.82	ALA	C	201	101.52	101.52	58.18
ALA	O	201	102.43	81.08	57.40	THR	N	202	100.47	100.47	57.79
THR	CA	202	100.31	79.51	56.44	THR	CB	202	100.84	100.84	56.46
THR	OG1	202	100.18	77.28	55.40	THR	CG2	202	100.74	100.74	57.87
THR	C	202	98.85	79.76	55.99	THR	O	202	97.86	97.86	56.73
ALA	N	203	98.77	80.32	54.78	ALA	CA	203	97.55	97.55	54.13
ALA	CB	203	97.62	81.95	53.42	ALA	C	203	97.21	97.21	53.06
ALA	O	203	98.01	79.39	52.10	SER	N	204	96.07	96.07	53.11
SER	CA	204	95.74	77.88	52.02	SER	CB	204	95.24	95.24	52.59
SER	OG	204	95.81	76.32	53.88	SER	C	204	94.68	94.68	51.11
SER	O	204	93.78	79.18	51.58	PHE	N	205	94.82	94.82	49.82
PHE	CA	205	93.88	78.71	48.82	PHE	CB	205	94.66	94.66	47.67
PHE	CG	205	95.39	80.58	48.21	PHE	CD1	205	96.69	96.69	48.74
PHE	CD2	205	94.71	81.79	48.26	PHE	CE1	205	97.29	97.29	49.31
PHE	CE2	205	95.32	82.90	48.83	PHE	CZ	205	96.60	96.60	49.36
PHE	C	205	93.10	77.48	48.39	PHE	O	205	93.61	93.61	47.71
ILE	N	206	91.86	77.39	48.88	ILE	CA	206	90.95	90.95	48.62
ILE	CB	206	90.21	75.94	49.92	ILE	CG2	206	89.07	89.07	49.73
ILE	CG1	206	91.24	75.32	50.82	ILE	CD1	206	90.96	90.96	52.30
ILE	C	206	90.02	76.83	47.57	ILE	O	206	89.43	89.43	47.79
TYR	N	207	89.91	76.22	46.42	TYR	CA	207	89.06	89.06	45.35
TYR	CB	207	89.83	77.19	44.20	TYR	CG	207	88.98	88.98	43.00
TYR	CD1	207	88.98	76.79	41.90	TYR	CE1	207	88.27	88.27	40.77
TYR	CD2	207	88.24	78.78	42.98	TYR	CE2	207	87.52	87.52	41.87
TYR	CZ	207	87.55	78.32	40.78	TYR	OH	207	86.85	86.85	39.65
TYR	C	207	88.34	75.43	44.87	TYR	O	207	88.92	88.92	44.46
ASP	N	208	87.03	75.66	44.79	ASP	CA	208	86.05	86.05	44.42
ASP	CB	208	86.36	74.17	43.05	ASP	CG	208	85.21	85.21	42.43
ASP	OD1	208	85.07	73.51	41.22	ASP	OD2	208	84.50	84.50	43.15
ASP	C	208	86.23	73.62	45.49	ASP	O	208	86.04	86.04	46.66
GLY	N	209	86.57	72.37	45.31	GLY	CA	209	86.76	86.76	46.50
GLY	C	209	88.18	71.51	47.07	GLY	O	209	88.41	88.41	48.27
ARG	N	210	89.10	71.61	46.12	ARG	CA	210	90.51	90.51	46.29
ARG	CB	210	91.23	71.29	44.94	ARG	CG	210	90.50	90.50	43.67
ARG	CD	210	89.78	69.60	43.81	ARG	NE	210	89.07	89.07	42.61
ARG	CZ	210	87.81	69.58	42.33	ARG	NH1	210	87.27	87.27	41.21
ARG	NH2	210	87.10	70.42	43.12	ARG	C	210	91.22	91.22	47.07
ARG	O	210	90.79	73.58	47.17	LEU	N	211	92.44	92.44	47.50
LEU	CA	211	93.37	73.07	48.08	LEU	CB	211	94.15	94.15	49.18
LEU	CG	211	94.86	73.40	50.09	LEU	CD1	211	94.78	94.78	51.55
LEU	CD2	211	96.27	73.46	49.61	LEU	C	211	94.21	94.21	46.82
LEU	O	211	94.75	72.23	46.38	VAL	N	212	94.25	94.25	46.12
VAL	CA	212	95.03	74.54	44.87	VAL	CB	212	94.19	94.19	43.84
VAL	CG1	212	94.91	75.55	42.51	VAL	CG2	212	92.93	92.93	43.50
VAL	C	212	96.40	75.23	45.10	VAL	O	212	97.23	97.23	44.20
ASP	N	213	96.73	75.81	46.28	ASP	CA	213	97.93	97.93	46.53
ASP	CB	213	97.89	77.90	45.73	ASP	CG	213	99.24	99.24	45.21
ASP	OD1	213	99.29	78.88	44.09	ASP	OD2	213	100.24	100.24	45.91
ASP	C	213	98.08	76.97	47.99	ASP	O	213	97.15	97.15	48.75
SER	N	214	99.20	77.53	48.41	SER	CA	214	99.39	99.39	49.76

FIGURE 1 (cont.)

SER	CB	214	99.70	76.86	50.71	SER	OG	214	100.73	100.73	50.13
SER	C	214	100.59	79.00	49.74	SER	O	214	101.28	101.28	48.70
ILE	N	215	100.81	79.70	50.86	ILE	CA	215	101.87	101.87	50.98
ILE	CB	215	101.38	82.03	50.35	ILE	CG2	215	100.62	100.62	51.29
ILE	CG1	215	102.64	82.65	49.83	ILE	CD1	215	102.45	102.45	49.05
ILE	C	215	102.20	80.83	52.45	ILE	O	215	101.30	101.30	53.28
GLY	N	216	103.45	81.09	52.84	GLY	CA	216	103.78	103.78	54.26
GLY	C	216	103.97	82.68	54.64	GLY	O	216	104.02	104.02	53.77
SER	N	217	104.04	82.97	55.94	SER	CA	217	104.28	104.28	56.54
SER	CB	217	104.50	84.09	58.01	SER	OG	217	104.24	104.24	58.80
SER	C	217	105.50	84.99	55.95	SER	O	217	106.60	106.60	56.08
TRP	N	218	105.42	86.13	55.26	TRP	CA	218	106.61	106.61	54.75
TRP	CB	218	106.32	87.60	53.49	TRP	CG	218	105.07	105.07	53.48
TRP	CD2	218	103.87	88.17	52.87	TRP	CE2	218	103.11	103.11	53.14
TRP	CE3	218	103.34	87.11	52.15	TRP	CD1	218	105.03	105.03	54.08
TRP	NE1	218	103.83	90.18	53.85	TRP	CZ2	218	101.81	101.81	52.69
TRP	CZ3	218	102.04	87.20	51.69	TRP	CH2	218	101.28	101.28	51.96
TRP	C	218	107.25	87.71	55.76	TRP	O	218	108.39	108.39	55.59
SER	N	219	106.63	88.15	56.84	SER	CA	219	107.28	107.28	57.77
SER	CB	219	106.61	90.43	57.88	SER	OG	219	106.58	106.58	56.70
SER	C	219	107.22	88.40	59.15	SER	O	219	107.45	107.45	60.15
GLN	N	220	106.92	87.11	59.25	GLN	CA	220	107.01	107.01	60.49
GLN	CB	220	108.51	86.22	60.82	GLN	CG	220	109.36	109.36	59.90
GLN	CD	220	109.53	85.76	58.44	GLN	OE1	220	109.30	109.30	57.49
GLN	NE2	220	109.96	86.97	58.09	GLN	E21	220	110.20	110.20	58.78
GLN	E22	220	109.97	87.15	57.12	GLN	C	220	106.27	106.27	61.65
GLN	O	220	106.61	86.88	62.82	ASN	N	221	105.17	105.17	61.33
ASN	CA	221	104.38	88.37	62.35	ASN	CB	221	105.03	105.03	62.72
ASN	CG	221	104.42	90.12	64.04	ASN	OD1	221	104.34	104.34	64.99
ASN	ND2	221	103.85	91.30	64.20	ASN	D21	221	103.72	103.72	63.43
ASN	D22	221	103.57	91.53	65.11	ASN	C	221	102.94	102.94	61.87
ASN	O	221	102.63	89.58	61.15	ILE	N	222	102.13	102.13	62.20
ILE	CA	222	100.71	87.40	61.95	ILE	CB	222	99.92	99.92	63.00
ILE	CG2	222	98.46	87.77	62.89	ILE	CG1	222	100.42	100.42	64.38
ILE	CD1	222	99.91	88.66	65.52	ILE	C	222	100.21	100.21	60.57
ILE	O	222	99.71	88.85	60.33	LEU	N	223	100.39	100.39	59.62
LEU	CA	223	99.89	87.03	58.25	LEU	CB	223	100.33	100.33	57.47
LEU	CG	223	99.90	85.55	56.06	LEU	CD1	223	100.38	100.38	55.14
LEU	CD2	223	100.43	84.18	55.70	LEU	C	223	98.36	98.36	58.36
LEU	O	223	97.78	86.37	59.07	ARG	N	224	97.68	97.68	57.74
ARG	CA	224	96.27	88.42	57.96	ARG	CB	224	95.98	95.98	58.80
ARG	CG	224	96.76	89.92	60.02	ARG	CD	224	97.22	97.22	59.96
ARG	NE	224	98.35	91.42	60.85	ARG	CZ	224	99.30	99.30	60.98
ARG	NH1	224	100.27	92.07	61.85	ARG	NH2	224	99.35	99.35	60.31
ARG	C	224	95.68	88.85	56.64	ARG	O	224	96.41	96.41	55.77
THR	N	225	94.35	88.75	56.52	THR	CA	225	93.64	93.64	55.35
THR	CB	225	93.50	88.05	54.42	THR	OG1	225	93.09	93.09	53.13
THR	CG2	225	92.60	87.00	55.02	THR	C	225	92.29	92.29	55.69
THR	O	225	91.93	90.18	56.88	GLN	N	226	91.56	91.56	54.59
GLN	CA	226	90.31	91.02	54.53	GLN	CB	226	89.61	89.61	53.27
GLN	CG	226	89.11	91.48	52.14	GLN	CD	226	90.18	90.18	51.12
GLN	OE1	226	90.11	91.59	49.88	GLN	NE2	226	91.27	91.27	51.73
GLN	E21	226	91.29	92.26	52.67	GLN	E22	226	92.04	92.04	51.13
GLN	C	226	89.34	90.87	55.70	GLN	O	226	89.05	89.05	56.37
GLU	N	227	88.88	89.65	56.02	GLU	CA	227	87.81	87.81	56.94
GLU	CB	227	87.95	89.87	58.32	GLU	CG	227	89.33	89.33	58.88
GLU	CD	227	89.81	88.30	59.17	GLU	OE1	227	89.31	89.31	58.60
GLU	OE2	227	90.70	88.16	60.01	GLU	C	227	86.48	86.48	56.40

FIGURE 1 (cont.)

GLU O	227	85.53	90.01	57.14	SER N	228	86.41	86.41	55.07
SER CA	228	85.22	90.05	54.34	SER CB	228	84.91	84.91	54.40
SER OG	228	85.71	92.50	53.68	SER C	228	85.52	85.52	52.91
SER O	228	86.60	89.13	52.58	GLU N	229	84.51	84.51	52.09
GLU CA	229	84.61	89.29	50.71	GLU CB	229	83.26	83.26	50.18
GLU CG	229	82.96	89.54	48.75	GLU CD	229	81.66	81.66	48.38
GLU OE1	229	81.58	91.42	48.46	GLU OE2	229	80.72	80.72	47.99
GLU C	229	85.80	89.80	49.87	GLU O	229	86.16	86.16	49.90
CYS N	230	86.31	88.93	49.03	CYS CA	230	87.31	87.31	48.04
CYS C	230	86.52	89.55	46.76	CYS O	230	85.28	85.28	46.75
CYS CB	230	88.28	88.06	47.89	CYS SG	230	87.72	87.72	47.82
VAL N	231	87.07	89.88	45.59	VAL CA	231	86.24	86.24	44.43
VAL CB	231	85.78	91.70	44.32	VAL CG1	231	86.20	86.20	45.53
VAL CG2	231	86.24	92.30	43.06	VAL C	231	87.03	87.03	43.24
VAL O	231	88.26	89.50	43.29	CYS N	232	86.34	86.34	42.18
CYS CA	232	86.92	88.46	41.09	CYS C	232	86.29	86.29	39.85
CYS O	232	85.07	89.32	39.78	CYS CB	232	86.56	86.56	41.21
CYS SG	232	86.76	86.12	42.83	ILE N	233	87.12	87.12	38.87
ILE CA	233	86.61	90.02	37.65	ILE CB	233	87.02	87.02	37.55
ILE CG2	233	86.36	92.07	36.32	ILE CG1	233	86.56	86.56	38.75
ILE CD1	233	86.81	93.83	38.58	ILE C	233	87.28	87.28	36.55
ILE O	233	88.49	89.06	36.51	ASN N	234	86.47	86.47	35.78
ASN CA	234	86.86	87.70	34.65	ASN CB	234	87.61	87.61	33.60
ASN CG	234	86.59	89.55	33.12	ASN OD1	234	85.67	85.67	32.33
ASN ND2	234	86.64	90.78	33.64	ASN D21	234	87.42	87.42	34.20
ASN D22	234	85.90	91.38	33.44	ASN C	234	87.68	87.68	34.96
ASN O	234	88.18	85.84	34.05	GLY N	235	87.69	87.69	36.21
GLY CA	235	88.46	84.86	36.54	GLY C	235	89.50	89.50	37.58
GLY O	235	89.84	84.28	38.38	THR N	236	90.00	90.00	37.70
THR CA	236	91.05	86.67	38.67	THR CB	236	92.02	92.02	38.01
THR OG1	236	92.25	87.16	36.68	THR CG2	236	93.31	93.31	38.79
THR C	236	90.44	87.23	39.93	THR O	236	89.68	89.68	39.84
CYS N	237	90.66	86.63	41.07	CYS CA	237	90.18	90.18	42.32
CYS C	237	91.35	87.87	42.95	CYS O	237	92.49	92.49	42.61
CYS CB	237	89.73	86.07	43.26	CYS SG	237	88.45	88.45	42.49
THR N	238	91.19	88.79	43.86	THR CA	238	92.32	92.32	44.36
THR CB	238	92.35	90.88	43.55	THR OG1	238	93.60	93.60	43.84
THR CG2	238	91.22	91.86	43.87	THR C	238	91.99	91.99	45.82
THR O	238	90.84	89.90	46.20	VAL N	239	92.94	92.94	46.66
VAL CA	239	92.71	89.49	48.09	VAL CB	239	92.75	92.75	48.78
VAL CG1	239	94.09	87.39	48.48	VAL CG2	239	92.71	92.71	50.29
VAL C	239	93.85	90.43	48.51	VAL O	239	94.80	94.80	47.75
VAL N	240	93.80	91.13	49.65	VAL CA	240	94.93	94.93	50.07
VAL CB	240	94.64	93.56	50.20	VAL CG1	240	93.67	93.67	49.12
VAL CG2	240	94.19	93.95	51.59	VAL C	240	95.22	95.22	51.43
VAL O	240	94.29	90.98	52.19	MET N	241	96.51	96.51	51.77
MET CA	241	96.97	90.51	52.96	MET CB	241	97.49	97.49	52.64
MET CG	241	96.47	88.09	52.29	MET SD	241	97.22	97.22	52.41
MET CE	241	96.97	86.19	50.69	MET C	241	98.12	98.12	53.54
MET O	241	98.82	92.02	52.81	THR N	242	98.31	98.31	54.86
THR CA	242	99.44	91.93	55.41	THR CB	242	99.03	99.03	55.95
THR OG1	242	98.78	93.30	57.34	THR CG2	242	97.76	97.76	55.33
THR C	242	100.09	91.08	56.52	THR O	242	99.43	99.43	57.23
ASP N	243	101.41	91.24	56.67	ASP CA	243	102.21	102.21	57.67
ASP CB	243	103.01	89.58	56.95	ASP CG	243	103.55	103.55	57.72
ASP OD1	243	103.79	87.44	57.00	ASP OD2	243	103.75	103.75	58.94
ASP C	243	103.09	91.66	58.21	ASP O	243	103.63	103.63	57.37
GLY N	244	103.31	91.83	59.50	GLY CA	244	104.13	104.13	59.94

FIGURE 1 (cont.)

GLY C	244	103.59	93.43	61.25	GLY O	244	102.86	102.86	61.96
SER N	245	103.92	94.67	61.60	SER CA	245	103.47	103.47	62.88
SER CB	245	104.40	96.26	63.33	SER OG	245	104.33	104.33	64.75
SER C	245	102.05	95.68	62.77	SER O	245	101.63	101.63	61.71
ALA N	246	101.36	95.65	63.91	ALA CA	246	99.98	99.98	64.01
ALA CB	246	99.32	95.53	65.26	ALA C	246	99.94	99.94	64.10
ALA O	246	99.32	98.23	63.25	SER N	247	100.64	100.64	65.07
SER CA	247	100.75	99.58	65.20	SER CB	247	100.20	100.20	66.56
SER OG	247	98.93	99.35	66.82	SER C	247	102.26	102.26	65.09
SER O	247	103.04	99.67	66.04	GLY N	248	102.60	102.60	63.81
GLY CA	248	103.93	100.11	63.30	GLY C	248	103.85	103.85	61.81
GLY O	248	102.79	99.50	61.30	ARG N	249	104.92	104.92	61.05
ARG CA	249	104.91	99.70	59.63	ARG CB	249	106.21	106.21	59.01
ARG CG	249	106.32	100.17	57.47	ARG CD	249	107.22	107.22	56.76
ARG NE	249	108.64	101.07	57.09	ARG CZ	249	109.32	109.32	57.77
ARG NH1	249	110.61	101.82	58.05	ARG NH2	249	108.73	108.73	58.17
ARG C	249	104.79	98.17	59.43	ARG O	249	105.24	105.24	60.25
ALA N	250	104.15	97.74	58.35	ALA CA	250	103.92	103.92	58.09
ALA CB	250	102.53	95.96	58.56	ALA C	250	104.02	104.02	56.59
ALA O	250	104.03	97.10	55.81	ASP N	251	104.07	104.07	56.21
ASP CA	251	104.22	94.49	54.83	ASP CB	251	105.25	105.25	54.76
ASP CG	251	105.88	93.14	53.41	ASP OD1	251	106.99	106.99	53.44
ASP OD2	251	105.29	93.44	52.36	ASP C	251	102.90	102.90	54.26
ASP O	251	102.42	92.92	54.64	THR N	252	102.37	102.37	53.33
THR CA	252	101.10	94.54	52.69	THR CB	252	100.22	100.22	52.81
THR OG1	252	100.03	96.13	54.20	THR CG2	252	98.88	98.88	52.13
THR C	252	101.32	94.19	51.24	THR O	252	102.05	102.05	50.54
ARG N	253	100.68	93.13	50.75	ARG CA	253	100.74	100.74	49.34
ARG CB	253	101.65	91.57	49.05	ARG CG	253	102.73	102.73	50.03
ARG CD	253	104.12	91.57	49.69	ARG NE	253	104.97	104.97	49.57
ARG CZ	253	106.04	90.15	50.33	ARG NH1	253	106.74	106.74	50.14
ARG NH2	253	106.47	90.98	51.28	ARG C	253	99.31	99.31	49.01
ARG O	253	98.49	92.06	49.88	ILE N	254	99.09	99.09	47.70
ILE CA	254	97.84	92.18	47.02	ILE CB	254	97.46	97.46	46.26
ILE CG2	254	96.34	93.22	45.27	ILE CG1	254	97.06	97.06	47.26
ILE CD1	254	98.25	95.43	47.68	ILE C	254	98.10	98.10	46.04
ILE O	254	98.85	91.18	45.06	LEU N	255	97.40	97.40	46.32
LEU CA	255	97.58	88.78	45.56	LEU CB	255	97.60	97.60	46.46
LEU CG	255	98.31	87.44	47.81	LEU CD1	255	98.79	98.79	47.83
LEU CD2	255	99.56	88.28	48.03	LEU C	255	96.42	96.42	44.62
LEU O	255	95.28	88.91	44.99	PHE N	256	96.76	96.76	43.40
PHE CA	256	95.89	88.12	42.29	PHE CB	256	96.42	96.42	41.05
PHE CG	256	96.51	90.27	41.20	PHE CD1	256	97.58	97.58	41.87
PHE CD2	256	95.48	91.05	40.69	PHE CE1	256	97.63	97.63	42.04
PHE CE2	256	95.55	92.42	40.87	PHE CZ	256	96.62	96.62	41.54
PHE C	256	95.92	86.61	42.11	PHE O	256	97.00	97.00	41.98
ILE N	257	94.76	85.96	42.05	ILE CA	257	94.69	94.69	42.01
ILE CB	257	94.56	84.00	43.52	ILE CG2	257	94.04	94.04	44.47
ILE CG1	257	93.72	82.76	43.52	ILE CD1	257	93.70	93.70	44.97
ILE C	257	93.64	83.95	41.08	ILE O	257	92.48	92.48	41.08
GLU N	258	94.04	83.00	40.26	GLU CA	258	93.19	93.19	39.25
GLU CB	258	93.83	82.52	37.90	GLU CG	258	93.64	93.64	37.50
GLU CD	258	94.37	84.40	36.25	GLU OE1	258	94.34	94.34	35.22
GLU OE2	258	94.97	85.47	36.35	GLU C	258	92.99	92.99	39.60
GLU O	258	93.95	80.23	39.81	GLU N	259	91.72	91.72	39.74
GLU CA	259	91.31	79.26	40.15	GLU CB	259	91.41	91.41	38.97
GLU CG	259	90.42	78.89	38.00	GLU CD	259	90.07	90.07	36.98
GLU OE1	259	90.64	77.83	35.89	GLU OE2	259	89.23	89.23	37.31

FIGURE 1 (cont.)

GLU C	259	92.07	78.68	41.33	GLU O	259	92.51	92.51	41.30
GLY N	260	92.27	79.44	42.41	GLY CA	260	93.00	93.00	43.55
GLY C	260	94.51	79.15	43.49	GLY O	260	95.18	95.18	44.54
LYS N	261	95.08	79.36	42.31	LYS CA	261	96.50	96.50	42.14
LYS CB	261	96.96	78.88	40.81	LYS CG	261	98.42	98.42	40.85
LYS CD	261	98.45	76.86	41.33	LYS CE	261	99.85	99.85	41.63
LYS NZ	261	100.09	76.25	43.08	LYS C	261	96.90	96.90	42.15
LYS O	261	96.37	81.81	41.38	ILE N	262	97.82	97.82	43.06
ILE CA	262	98.37	82.69	43.14	ILE CB	262	99.33	99.33	44.33
ILE CG2	262	99.91	84.21	44.37	ILE CG1	262	98.61	98.61	45.62
ILE CD1	262	99.56	82.60	46.83	ILE C	262	99.11	99.11	41.85
ILE O	262	100.16	82.39	41.61	VAL N	263	98.62	98.62	40.96
VAL CA	263	99.29	84.10	39.72	VAL CB	263	98.31	98.31	38.54
VAL CG1	263	97.61	82.89	38.37	VAL CG2	263	97.31	97.31	38.77
VAL C	263	100.13	85.38	39.76	VAL O	263	100.85	100.85	38.79
HIS N	264	100.04	86.24	40.78	HIS CA	264	100.81	100.81	40.83
HIS CB	264	100.26	88.50	39.86	HIS CG	264	101.24	101.24	39.65
HIS CD2	264	101.89	89.88	38.47	HIS ND1	264	101.69	101.69	40.52
HIS CE1	264	102.59	91.32	39.93	HIS NE2	264	102.69	102.69	38.70
HIS C	264	100.67	88.00	42.22	HIS O	264	99.66	99.66	42.86
ILE N	265	101.66	88.72	42.73	ILE CA	265	101.61	101.61	44.03
ILE CB	265	102.53	88.64	44.99	ILE CG2	265	102.54	102.54	46.28
ILE CG1	265	102.07	87.17	45.15	ILE CD1	265	102.61	102.61	46.37
ILE C	265	102.13	90.77	43.73	ILE O	265	103.03	103.03	42.90
SER N	266	101.51	91.83	44.26	SER CA	266	101.90	101.90	44.06
SER CB	266	100.86	93.87	43.21	SER OG	266	100.99	100.99	41.92
SER C	266	101.99	93.87	45.43	SER O	266	101.07	101.07	46.24
PRO N	267	103.12	94.49	45.80	PRO CD	267	104.36	104.36	45.04
PRO CA	267	103.28	95.20	47.07	PRO CB	267	104.77	104.77	47.21
PRO CG	267	105.18	95.53	45.77	PRO C	267	102.47	102.47	46.98
PRO O	267	102.20	96.98	45.87	LEU N	268	102.16	102.16	48.18
LEU CA	268	101.25	98.09	48.31	LEU CB	268	101.07	101.07	49.79
LEU CG	268	100.13	99.56	50.17	LEU CD1	268	98.73	98.73	49.57
LEU CD2	268	100.10	99.61	51.68	LEU C	268	101.53	101.53	47.54
LEU O	268	100.81	99.42	46.56	ALA N	269	102.40	102.40	47.75
ALA CA	269	102.39	101.58	46.91	ALA CB	269	102.40	102.40	45.36
ALA C	269	101.21	102.57	47.10	ALA O	269	100.03	100.03	47.28
GLY N	270	101.59	103.86	46.94	GLY CA	270	100.75	100.75	47.12
GLY C	270	101.00	105.64	48.50	GLY O	270	101.99	101.99	49.16
SER N	271	100.05	106.47	48.94	SER CA	271	100.09	100.09	50.16
SER CB	271	99.00	108.41	50.18	SER OG	271	98.46	98.46	49.00
SER C	271	99.87	106.54	51.48	SER O	271	100.29	100.29	52.54
ALA N	272	99.15	105.41	51.46	ALA CA	272	98.66	98.66	52.69
ALA CB	272	97.64	103.68	52.33	ALA C	272	99.76	99.76	53.56
ALA O	272	100.69	103.53	53.08	GLN N	273	99.69	99.69	54.85
GLN CA	273	100.74	104.06	55.75	GLN CB	273	100.89	100.89	56.84
GLN CG	273	101.42	106.39	56.28	GLN CD	273	102.92	102.92	56.12
GLN OE1	273	103.64	106.68	57.06	GLN NE2	273	103.43	103.43	54.94
GLN E21	273	102.87	105.80	54.16	GLN E22	273	104.41	104.41	54.92
GLN C	273	100.61	102.74	56.42	GLN O	273	101.63	101.63	56.86
HIS N	274	99.39	102.21	56.59	HIS CA	274	99.17	99.17	57.25
HIS CB	274	99.20	101.15	58.75	HIS CG	274	99.31	99.31	59.51
HIS CD2	274	98.25	99.19	60.09	HIS ND1	274	100.41	100.41	59.75
HIS CE1	274	100.06	98.11	60.46	HIS NE2	274	98.77	98.77	60.66
HIS C	274	97.80	100.42	56.81	HIS O	274	96.82	96.82	57.01
VAL N	275	97.73	99.23	56.22	VAL CA	275	96.52	96.52	55.74
VAL CB	275	96.71	98.33	54.27	VAL CG1	275	95.54	95.54	53.71
VAL CG2	275	96.82	99.66	53.54	VAL C	275	96.27	96.27	56.54

FIGURE 1 (cont.)

VAL	O	275	97.11	96.44	56.77	:	GLU	N	276	95.07	95.07	57.03
GLU	CA	276	94.63	96.10	57.88	:	GLU	CB	276	94.87	94.87	59.24
GLU	CG	276	95.02	95.96	60.54	:	GLU	CD	276	96.30	96.30	60.73
GLU	OE1	276	96.78	95.05	61.87	:	GLU	OE2	276	96.81	96.81	59.72
GLU	C	276	93.16	95.88	57.42	:	GLU	O	276	92.54	92.54	56.90
GLU	N	277	92.57	94.69	57.47	:	GLU	CA	277	91.17	91.17	57.15
GLU	CB	277	90.41	94.51	58.45	:	GLU	CG	277	90.95	90.95	59.50
GLU	CD	277	90.61	94.02	60.92	:	GLU	OE1	277	90.85	90.85	61.88
GLU	OE2	277	90.11	95.12	61.13	:	GLU	C	277	90.42	90.42	56.00
GLU	O	277	89.41	95.74	56.21	:	CYS	N	278	90.86	90.86	54.75
CYS	CA	278	90.14	95.67	53.71	:	CYS	C	278	88.72	88.72	53.43
CYS	O	278	88.42	94.01	53.58	:	CYS	CB	278	90.94	90.94	52.43
CYS	SG	278	92.42	96.65	52.61	:	SER	N	279	87.90	87.90	52.95
SER	CA	279	86.54	95.94	52.57	:	SER	CB	279	85.70	85.70	53.43
SER	OG	279	85.61	96.26	54.74	:	SER	C	279	86.60	86.60	51.13
SER	O	279	86.66	97.54	50.81	:	CYS	N	280	86.71	86.71	50.25
CYS	CA	280	86.92	95.67	48.86	:	CYS	C	280	85.61	85.61	48.13
CYS	O	280	84.69	94.89	48.72	:	CYS	CB	280	88.04	88.04	48.36
CYS	SG	280	89.56	94.89	49.35	:	TYR	N	281	85.49	85.49	46.90
TYR	CA	281	84.25	95.94	46.17	:	TYR	CB	281	83.19	83.19	46.72
TYR	CG	281	83.55	98.51	46.72	:	TYR	CD1	281	83.97	83.97	47.89
TYR	CE1	281	84.27	100.50	47.88	:	TYR	CD2	281	83.42	83.42	45.53
TYR	CE2	281	83.72	100.56	45.51	:	TYR	CZ	281	84.13	84.13	46.68
TYR	OH	281	84.40	102.55	46.59	:	TYR	C	281	84.56	84.56	44.71
TYR	O	281	85.50	96.91	44.39	:	PRO	N	282	83.86	83.86	43.76
PRO	CD	282	82.89	94.50	43.98	:	PRO	CA	282	84.11	84.11	42.36
PRO	CB	282	83.31	94.69	41.67	:	PRO	CG	282	82.19	82.19	42.63
PRO	C	282	83.71	97.18	41.94	:	PRO	O	282	82.66	82.66	42.35
ARG	N	283	84.55	97.77	41.10	:	ARG	CA	283	84.36	84.36	40.50
ARG	CB	283	85.16	100.13	41.25	:	ARG	CG	283	84.36	84.36	41.89
ARG	CD	283	85.38	102.26	42.36	:	ARG	NE	283	85.79	85.79	41.22
ARG	CZ	283	85.14	104.16	40.85	:	ARG	NH1	283	85.53	85.53	39.79
ARG	NH2	283	84.09	104.60	41.54	:	ARG	C	283	84.90	84.90	39.10
ARG	O	283	85.86	99.63	38.76	:	TYR	N	284	84.36	84.36	38.34
TYR	CA	284	84.76	97.72	36.98	:	TYR	CB	284	83.56	83.56	36.15
TYR	CG	284	84.04	96.61	34.88	:	TYR	CD1	284	84.08	84.08	33.71
TYR	CE1	284	84.61	96.72	32.58	:	TYR	CD2	284	84.53	84.53	34.92
TYR	CE2	284	85.07	94.72	33.81	:	TYR	CZ	284	85.11	85.11	32.65
TYR	OH	284	85.70	94.89	31.53	:	TYR	C	284	85.40	85.40	36.25
TYR	O	284	84.72	99.90	36.10	:	PRO	N	285	86.63	86.63	35.74
PRO	CD	285	87.22	99.90	34.95	:	PRO	CA	285	87.44	87.44	35.65
PRO	CB	285	88.18	97.83	34.36	:	PRO	CG	285	88.53	88.53	34.48
PRO	C	285	88.33	97.32	36.83	:	PRO	O	285	89.15	89.15	36.72
GLY	N	286	88.19	98.00	37.95	:	GLY	CA	286	89.09	89.09	39.05
GLY	C	286	88.33	97.25	40.23	:	GLY	O	286	87.13	87.13	40.17
VAL	N	287	89.03	97.21	41.33	:	VAL	CA	287	88.51	88.51	42.61
VAL	CB	287	89.19	95.47	43.00	:	VAL	CG1	287	88.77	88.77	44.37
VAL	CG2	287	88.83	94.41	41.97	:	VAL	C	287	88.96	88.96	43.51
VAL	O	287	90.03	98.52	43.22	:	ARG	N	288	88.26	88.26	44.58
ARG	CA	288	88.71	99.41	45.42	:	ARG	CB	288	87.87	87.87	45.03
ARG	CG	288	87.68	101.70	46.12	:	ARG	CD	288	88.13	88.13	45.78
ARG	NE	288	87.16	103.85	45.00	:	ARG	CZ	288	87.53	87.53	43.96
ARG	NH1	288	86.64	105.38	43.33	:	ARG	NH2	288	88.75	88.75	43.47
ARG	C	288	88.49	98.95	46.85	:	ARG	O	288	87.47	87.47	47.15
CYS	N	289	89.32	99.29	47.83	:	CYS	CA	289	89.11	89.11	49.17
CYS	C	289	89.15	99.93	50.17	:	CYS	O	289	89.86	89.86	49.90
CYS	CB	289	90.21	97.78	49.52	:	CYS	SG	289	90.43	90.43	48.35
ILE	N	290	88.43	99.90	51.29	:	ILE	CA	290	88.54	88.54	52.33

FIGURE 1 (cont.)

ILE	CB	290	87.15	101.64	52.57	: ILE	CG2	290	86.98	86.98	54.02
ILE	CG1	290	87.09	102.90	51.72	: ILE	CD1	290	87.05	87.05	50.18
ILE	C	290	88.98	100.04	53.48	: ILE	O	290	88.31	88.31	53.84
CYS	N	291	90.12	100.36	54.09	: CYS	CA	291	90.74	90.74	55.01
CYS	C	291	90.93	100.07	56.35	: CYS	O	291	90.36	90.36	56.57
CYS	CB	291	92.05	99.00	54.42	: CYS	SG	291	91.90	91.90	52.65
ARG	N	292	91.64	99.49	57.30	: ARG	CA	292	91.80	91.80	58.64
ARG	CB	292	91.51	98.94	59.66	: ARG	CG	292	91.64	91.64	61.04
ARG	CD	292	92.33	98.55	62.02	: ARG	NE	292	91.57	91.57	62.32
ARG	CZ	292	91.52	96.83	63.56	: ARG	NH1	292	90.76	90.76	63.81
ARG	NH2	292	92.19	97.34	64.60	: ARG	C	292	93.26	93.26	58.72
ARG	O	292	94.12	99.78	58.12	: ASP	N	293	93.51	93.51	59.39
ASP	CA	293	94.84	102.00	59.74	: ASP	CB	293	95.10	95.10	59.15
ASP	CG	293	96.47	103.96	59.45	: ASP	OD1	293	96.82	96.82	60.61
ASP	OD2	293	97.19	104.39	58.55	: ASP	C	293	94.81	94.81	61.27
ASP	O	293	94.10	102.79	62.09	: ASN	N	294	95.83	95.83	61.54
ASN	CA	294	96.13	100.84	62.89	: ASN	CB	294	96.36	96.36	62.92
ASN	CG	294	95.75	98.76	64.18	: ASN	OD1	294	94.53	94.53	64.25
ASN	ND2	294	96.49	98.49	65.26	: ASN	D21	294	97.43	97.43	65.27
ASN	D22	294	96.06	98.03	66.00	: ASN	C	294	97.27	97.27	63.60
ASN	O	294	97.44	101.37	64.81	: TRP	N	295	97.96	97.96	62.87
TRP	CA	295	99.14	103.19	63.32	: TRP	CB	295	100.41	100.41	62.83
TRP	CG	295	101.77	103.21	62.79	: TRP	CD2	295	102.57	102.57	61.67
TRP	CE2	295	103.73	103.90	62.22	: TRP	CE3	295	102.49	102.49	60.32
TRP	CD1	295	102.40	103.64	63.93	: TRP	NE1	295	103.59	103.59	63.54
TRP	CZ2	295	104.80	104.19	61.43	: TRP	CZ3	295	103.56	103.56	59.51
TRP	CH2	295	104.71	103.97	60.07	: TRP	C	295	99.04	99.04	62.65
TRP	O	295	99.21	104.61	61.42	: LYS	N	296	98.75	98.75	63.41
LYS	CA	296	98.68	106.99	62.88	: LYS	CB	296	99.94	99.94	61.96
LYS	CG	296	101.32	107.12	62.63	: LYS	CD	296	102.64	102.64	62.08
LYS	CE	296	102.86	107.74	60.56	: LYS	NZ	296	102.53	102.53	59.94
LYS	C	296	97.40	107.39	62.12	: LYS	O	296	97.28	97.28	61.68
GLY	N	297	96.35	106.56	62.02	: GLY	CA	297	95.11	95.11	61.32
GLY	C	297	93.75	106.50	61.91	: GLY	O	297	93.48	93.48	62.45
SER	N	298	92.96	107.58	61.84	: SER	CA	298	91.53	91.53	62.14
SER	CB	298	91.06	108.78	62.97	: SER	OG	298	91.73	91.73	64.19
SER	C	298	90.85	107.80	60.80	: SER	O	298	89.68	89.68	60.70
ASN	N	299	91.46	108.38	59.77	: ASN	CA	299	90.83	90.83	58.46
ASN	CB	299	91.38	109.53	57.53	: ASN	CG	299	92.87	92.87	57.58
ASN	OD1	299	93.54	109.68	58.60	: ASN	ND2	299	93.45	93.45	56.51
ASN	D21	299	92.89	110.65	55.74	: ASN	D22	299	94.43	94.43	56.51
ASN	C	299	91.13	107.00	57.86	: ASN	O	299	92.07	92.07	58.31
ARG	N	300	90.34	106.53	56.88	: ARG	CA	300	90.46	90.46	56.42
ARG	CB	300	89.04	104.51	56.19	: ARG	CG	300	88.17	88.17	57.46
ARG	CD	300	86.94	103.45	57.47	: ARG	NE	300	87.43	87.43	57.87
ARG	CZ	300	87.46	101.74	59.12	: ARG	NH1	300	88.21	88.21	59.34
ARG	NH2	300	86.71	102.19	60.11	: ARG	C	300	91.26	91.26	55.15
ARG	O	300	91.03	105.96	54.27	: PRO	N	301	92.25	92.25	55.05
PRO	CD	301	92.79	103.51	56.21	: PRO	CA	301	93.07	93.07	53.88
PRO	CB	301	93.94	102.80	54.26	: PRO	CG	301	94.09	94.09	55.75
PRO	C	301	92.28	103.65	52.67	: PRO	O	301	91.28	91.28	52.84
VAL	N	302	92.65	104.01	51.46	: VAL	CA	302	91.93	91.93	50.27
VAL	CB	302	91.52	104.72	49.39	: VAL	CG1	302	91.01	91.01	48.01
VAL	CG2	302	90.51	105.48	50.20	: VAL	C	302	92.95	92.95	49.51
VAL	O	302	94.11	103.16	49.45	: VAL	N	303	92.67	92.67	48.90
VAL	CA	303	93.62	100.81	48.12	: VAL	CB	303	93.95	93.95	48.78
VAL	CG1	303	94.85	98.70	47.80	: VAL	CG2	303	94.63	94.63	50.16
VAL	C	303	92.93	100.58	46.81	: VAL	O	303	91.83	91.83	46.81

FIGURE 1 (cont.)

ASP	N	304	93.55	100.94	45.72	ASP	CA	304	93.00	93.00 44.42
ASP	CB	304	92.94	102.12	43.73	ASP	CG	304	91.58	91.58 43.98
ASP	OD1	304	91.43	103.49	44.97	ASP	OD2	304	90.67	90.67 43.19
ASP	C	304	93.82	99.79	43.61	ASP	O	304	95.04	95.04 43.47
ILE	N	305	93.16	98.80	43.01	ILE	CA	305	93.80	93.80 42.36
ILE	CB	305	93.29	96.41	43.09	ILE	CG2	305	93.67	93.67 42.39
ILE	CG1	305	93.85	96.46	44.50	ILE	CD1	305	92.88	92.88 45.63
ILE	C	305	93.43	97.69	40.89	ILE	O	305	92.25	92.25 40.55
ASN	N	306	94.41	97.62	39.99	ASN	CA	306	94.16	94.16 38.56
ASN	CB	306	95.24	98.50	37.83	ASN	CG	306	95.09	95.09 36.31
ASN	OD1	306	94.74	97.63	35.64	ASN	ND2	306	95.38	95.38 35.65
ASN	D21	306	95.75	100.47	36.17	ASN	D22	306	95.22	95.22 34.69
ASN	C	306	94.23	96.23	38.09	ASN	O	306	95.31	95.31 38.01
MET	N	307	93.10	95.67	37.70	MET	CA	307	93.11	93.11 37.42
MET	CB	307	91.69	93.70	37.31	MET	CG	307	90.80	90.80 38.52
MET	SD	307	91.50	93.06	39.98	MET	CE	307	90.92	90.92 39.81
MET	C	307	93.85	93.97	36.14	MET	O	307	94.36	94.36 36.03
GLU	N	308	93.96	94.91	35.20	GLU	CA	308	94.74	94.74 33.99
GLU	CB	308	94.29	95.66	32.92	GLU	CG	308	92.87	92.87 32.45
GLU	CD	308	91.93	96.53	32.22	GLU	OE1	308	91.26	91.26 31.17
GLU	OE2	308	91.86	97.41	33.10	GLU	C	308	96.25	96.25 34.21
GLU	O	308	97.01	93.91	33.82	ASP	N	309	96.79	96.79 34.84
ASP	CA	309	98.23	95.95	35.02	ASP	CB	309	98.76	98.76 35.29
ASP	CG	309	98.32	98.57	34.53	ASP	OD1	309	98.07	98.07 33.32
ASP	OD2	309	98.27	99.63	35.15	ASP	C	309	98.76	98.76 36.24
ASP	O	309	99.96	94.99	36.32	TYR	N	310	97.92	97.92 37.24
TYR	CA	310	98.28	94.46	38.57	TYR	CB	310	99.26	99.26 38.56
TYR	CG	310	98.76	92.04	37.77	TYR	CD1	310	99.53	99.53 36.76
TYR	CE1	310	99.08	90.41	36.05	TYR	CD2	310	97.55	97.55 38.07
TYR	CE2	310	97.09	90.39	37.37	TYR	CZ	310	97.86	97.86 36.37
TYR	OH	310	97.42	88.73	35.70	TYR	C	310	98.94	98.94 39.40
TYR	O	310	99.62	95.29	40.41	SER	N	311	98.74	98.74 38.97
SER	CA	311	99.22	97.97	39.69	SER	CB	311	99.39	99.39 38.74
SER	OG	311	98.40	99.23	37.73	SER	C	311	98.32	98.32 40.85
SER	O	311	97.09	98.37	40.75	ILE	N	312	98.93	98.93 41.95
ILE	CA	312	98.25	99.26	43.16	ILE	CB	312	98.84	98.84 44.36
ILE	CG2	312	98.02	98.76	45.60	ILE	CG1	312	98.85	98.85 44.08
ILE	CD1	312	97.55	96.35	43.56	ILE	C	312	98.47	98.47 43.28
ILE	O	312	99.34	101.37	42.61	ASP	N	313	97.59	97.59 44.04
ASP	CA	313	97.62	102.83	44.39	ASP	CB	313	96.79	96.79 43.43
ASP	CG	313	96.85	105.22	43.60	ASP	OD1	313	97.53	97.53 44.51
ASP	OD2	313	96.19	105.93	42.82	ASP	C	313	96.96	96.96 45.75
ASP	O	313	96.16	101.98	46.08	SER	N	314	97.23	97.23 46.61
SER	CA	314	96.53	103.88	47.86	SER	CB	314	97.30	97.30 48.87
SER	OG	314	98.46	103.65	49.42	SER	C	314	96.46	96.46 48.24
SER	O	314	97.36	106.12	47.84	SER	N	315	95.50	95.50 49.10
SER	CA	315	95.18	107.15	49.52	SER	CB	315	94.11	94.11 48.66
SER	OG	315	94.10	107.40	47.29	SER	C	315	94.56	94.56 50.89
SER	O	315	94.75	105.99	51.53	TYR	N	316	93.88	93.88 51.38
TYR	CA	316	93.01	108.03	52.54	TYR	CB	316	93.56	93.56 53.66
TYR	CG	316	94.66	108.00	54.33	TYR	CD1	316	94.37	94.37 55.53
TYR	CE1	316	95.33	106.69	56.18	TYR	CD2	316	95.92	95.92 53.75
TYR	CE2	316	96.89	107.15	54.39	TYR	CZ	316	96.57	96.57 55.59
TYR	OH	316	97.46	105.75	56.23	TYR	C	316	91.67	91.67 52.12
TYR	O	316	91.62	109.47	51.21	VAL	N	317	90.51	90.51 52.72
VAL	CA	317	89.21	108.81	52.24	VAL	CB	317	87.98	87.98 52.90
VAL	CG1	317	88.00	106.59	52.45	VAL	CG2	317	88.07	88.07 54.40
VAL	C	317	89.13	110.29	52.54	VAL	O	317	89.41	89.41 53.69

FIGURE 1 (cont.)

CYS N	318	88.79	111.12	51.55	:	CYS CA	318	88.77	88.77	51.74
CYS C	318	87.94	113.14	52.88	:	CYS O	318	88.41	88.41	53.57
CYS CB	318	88.30	113.28	50.50	:	CYS SG	318	89.55	89.55	49.20
SER N	319	86.72	112.65	53.11	:	SER CA	319	85.83	85.83	54.17
SER CB	319	84.87	111.88	54.51	:	SER OG	319	84.27	84.27	55.83
SER C	319	86.50	113.49	55.45	:	SER O	319	87.31	87.31	56.05
GLY N	320	86.15	114.67	55.94	:	GLY CA	320	86.63	86.63	57.23
GLY C	320	85.91	114.39	58.31	:	GLY O	320	86.33	86.33	59.47
LEU N	321	84.79	113.73	57.95	:	LEU CA	321	83.99	83.99	58.91
LEU CB	321	82.56	112.84	58.39	:	LEU CG	321	81.69	81.69	58.62
LEU CD1	321	80.31	113.95	57.97	:	LEU CD2	321	81.58	81.58	60.12
LEU C	321	84.61	111.67	59.24	:	LEU O	321	84.25	84.25	60.32
VAL N	322	85.49	110.93	58.58	:	VAL CA	322	86.30	86.30	59.29
VAL CB	322	87.29	110.79	60.24	:	VAL CG1	322	87.95	87.95	61.34
VAL CG2	322	88.44	111.35	59.37	:	VAL C	322	85.64	85.64	60.02
VAL O	322	84.99	108.80	61.06	:	GLY N	323	86.05	86.05	59.53
GLY CA	323	85.40	106.30	59.81	:	GLY C	323	86.00	86.00	60.88
GLY O	323	85.29	104.49	61.28	:	ASP N	324	87.22	87.22	61.37
ASP CA	324	87.73	104.63	62.33	:	ASP CB	324	89.25	89.25	62.33
ASP CG	324	90.01	103.38	62.16	:	ASP OD1	324	89.61	89.61	62.80
ASP OD2	324	90.97	103.37	61.38	:	ASP C	324	87.22	87.22	63.72
ASP O	324	86.61	105.91	63.96	:	THR N	325	87.51	87.51	64.64
THR CA	325	87.25	104.14	66.07	:	THR CB	325	86.07	86.07	66.50
THR OG1	325	85.06	103.57	65.54	:	THR CG2	325	85.59	85.59	67.88
THR C	325	88.54	103.59	66.69	:	THR O	325	88.94	88.94	66.28
PRO N	326	89.33	104.25	67.58	:	PRO CD	326	90.52	90.52	68.20
PRO CA	326	89.14	105.63	68.02	:	PRO CB	326	90.20	90.20	69.06
PRO CG	326	90.53	104.41	69.53	:	PRO C	326	89.22	89.22	66.91
PRO O	326	89.83	106.47	65.85	:	ARG N	327	88.57	88.57	67.21
ARG CA	327	88.32	108.87	66.29	:	ARG CB	327	87.00	87.00	65.66
ARG CG	327	86.58	109.45	64.50	:	ARG CD	327	85.04	85.04	64.27
ARG NE	327	84.47	108.12	64.25	:	ARG CZ	327	83.40	83.40	64.99
ARG NH1	327	82.98	106.54	65.00	:	ARG NH2	327	82.68	82.68	65.69
ARG C	327	88.25	110.10	67.21	:	ARG O	327	87.92	87.92	68.39
ASN N	328	88.45	111.32	66.71	:	ASN CA	328	88.50	88.50	67.55
ASN CB	328	89.27	113.63	66.85	:	ASN CG	328	90.64	90.64	67.46
ASN OD1	328	91.03	113.31	68.50	:	ASN ND2	328	91.43	91.43	66.79
ASN D21	328	91.09	115.07	65.97	:	ASN D22	328	92.33	92.33	67.15
ASN C	328	87.18	113.11	68.01	:	ASN O	328	87.00	87.00	69.22
ASP N	329	86.30	113.50	67.09	:	ASP CA	329	85.00	85.00	67.33
ASP CB	329	85.00	115.14	68.54	:	ASP CG	329	84.48	84.48	68.41
ASP OD1	329	85.27	117.48	68.62	:	ASP OD2	329	83.30	83.30	68.11
ASP C	329	84.89	114.91	66.03	:	ASP O	329	85.91	85.91	65.46
ASP N	330	83.68	115.14	65.55	:	ASP CA	330	83.56	83.56	64.22
ASP CB	330	82.13	115.49	63.72	:	ASP CG	330	81.71	81.71	63.52
ASP OD1	330	82.47	113.08	63.72	:	ASP OD2	330	80.56	80.56	63.14
ASP C	330	83.94	117.12	64.10	:	ASP O	330	84.15	84.15	62.99
ARG N	331	83.98	117.82	65.23	:	ARG CA	331	84.44	84.44	65.21
ARG CB	331	84.26	119.94	66.53	:	ARG CG	331	82.87	82.87	67.10
ARG CD	331	82.75	121.50	67.67	:	ARG NE	331	82.71	82.71	66.60
ARG CZ	331	82.56	123.83	66.81	:	ARG NH1	331	82.55	82.55	65.75
ARG NH2	331	82.42	124.36	68.04	:	ARG C	331	85.93	85.93	64.99
ARG O	331	86.43	119.77	64.07	:	SER N	332	86.64	86.64	65.80
SER CA	332	88.08	118.35	65.70	:	SER CB	332	88.57	88.57	67.13
SER OG	332	87.90	117.25	67.86	:	SER C	332	88.65	88.65	64.81
SER O	332	89.66	116.65	65.23	:	SER N	333	88.13	88.13	63.62
SER CA	333	88.72	115.79	62.93	:	SER CB	333	87.78	87.78	62.95
SER OG	333	86.64	114.60	62.13	:	SER C	333	89.08	89.08	61.52

FIGURE 1 (cont.)

SER	O	333	88.50	117.07	60.92	:	ASN	N	334	90.01	90.01	60.87
ASN	CA	334	90.50	115.87	59.58	:	ASN	CB	334	91.68	91.68	59.66
ASN	CG	334	91.35	118.17	60.38	:	ASN	OD1	334	91.50	91.50	61.61
ASN	ND2	334	90.87	119.15	59.63	:	ASN	D21	334	90.74	90.74	58.66
ASN	D22	334	90.64	119.98	60.08	:	ASN	C	334	91.00	91.00	58.79
ASN	O	334	91.40	113.69	59.31	:	SER	N	335	90.94	90.94	57.51
SER	CA	335	91.53	114.11	56.52	:	SER	CB	335	90.60	90.60	56.01
SER	OG	335	91.28	112.13	55.10	:	SER	C	335	91.80	91.80	55.37
SER	O	335	90.99	115.96	55.08	:	ASN	N	336	92.95	92.95	54.73
ASN	CA	336	93.34	115.67	53.57	:	ASN	CB	336	94.71	94.71	53.74
ASN	CG	336	95.85	115.26	53.89	:	ASN	OD1	336	95.73	95.73	53.78
ASN	ND2	336	97.06	115.75	54.15	:	ASN	D21	336	97.18	97.18	54.17
ASN	D22	336	97.78	115.12	54.31	:	ASN	C	336	93.41	93.41	52.38
ASN	O	336	94.00	115.14	51.37	:	CYS	N	337	92.90	92.90	52.51
CYS	CA	337	92.90	112.49	51.46	:	CYS	C	337	94.24	94.24	51.11
CYS	O	337	94.30	110.89	50.30	:	CYS	CB	337	92.37	92.37	50.15
CYS	SG	337	91.00	114.22	50.37	:	ARG	N	338	95.34	95.34	51.65
ARG	CA	338	96.69	111.95	51.28	:	ARG	CB	338	97.51	97.51	50.88
ARG	CG	338	97.49	113.92	49.49	:	ARG	CD	338	98.07	98.07	49.36
ARG	NE	338	99.39	115.57	49.96	:	ARG	CZ	338	99.55	99.55	51.30
ARG	NH1	338	100.76	115.62	51.88	:	ARG	NH2	338	98.51	98.51	52.08
ARG	C	338	97.41	111.25	52.44	:	ARG	O	338	98.02	98.02	52.23
ASP	N	339	97.36	111.68	53.70	:	ASP	CA	339	98.23	98.23	54.70
ASP	CB	339	99.29	112.14	55.18	:	ASP	CG	339	99.87	99.87	54.09
ASP	OD1	339	100.37	112.53	53.07	:	ASP	OD2	339	99.79	99.79	54.24
ASP	C	339	97.40	110.60	55.87	:	ASP	O	339	96.29	96.29	56.03
PRO	N	340	97.81	109.66	56.72	:	PRO	CD	340	99.00	99.00	56.59
PRO	CA	340	97.22	109.45	58.03	:	PRO	CB	340	98.17	98.17	58.78
PRO	CG	340	99.46	108.72	58.06	:	PRO	C	340	97.07	97.07	58.71
PRO	O	340	98.00	111.54	58.86	:	ASN	N	341	95.87	95.87	59.10
ASN	CA	341	95.58	112.31	59.78	:	ASN	CB	341	94.07	94.07	60.05
ASN	CG	341	93.39	111.48	61.02	:	ASN	OD1	341	93.97	93.97	61.69
ASN	ND2	341	92.08	111.52	61.15	:	ASN	D21	341	91.61	91.61	60.57
ASN	D22	341	91.67	110.94	61.80	:	ASN	C	341	96.31	96.31	61.11
ASN	O	341	96.30	113.46	61.73	:	ASN	N	342	96.90	96.90	61.64
ASN	CA	342	97.59	111.37	62.92	:	ASN	CB	342	98.80	98.80	62.87
ASN	CG	342	100.04	111.56	62.48	:	ASN	OD1	342	100.66	100.66	63.35
ASN	ND2	342	100.42	111.57	61.19	:	ASN	D21	342	99.86	99.86	60.53
ASN	D22	342	101.25	111.11	60.96	:	ASN	C	342	96.76	96.76	64.10
ASN	O	342	97.32	111.95	65.19	:	GLU	N	343	95.43	95.43	63.92
GLU	CA	343	94.55	112.36	64.97	:	GLU	CB	343	93.18	93.18	64.47
GLU	CG	343	93.04	114.17	64.39	:	GLU	CD	343	92.49	92.49	63.05
GLU	OE1	343	91.46	114.02	62.70	:	GLU	OE2	343	93.10	93.10	62.35
GLU	C	343	94.39	111.38	66.07	:	GLU	O	343	95.10	95.10	67.06
ARG	N	344	93.54	110.36	66.05	:	ARG	CA	344	93.60	93.60	67.18
ARG	CB	344	92.25	109.52	67.83	:	ARG	CG	344	92.53	92.53	69.29
ARG	CD	344	91.28	110.04	69.95	:	ARG	NE	344	90.98	90.98	71.07
ARG	CZ	344	89.72	108.83	71.39	:	ARG	NH1	344	89.54	89.54	72.42
ARG	NH2	344	88.66	109.33	70.74	:	ARG	C	344	93.98	93.98	66.58
ARG	O	344	93.37	107.05	66.75	:	GLY	N	345	95.06	95.06	65.81
GLY	CA	345	95.63	107.18	64.94	:	GLY	C	345	95.46	95.46	65.14
GLY	O	345	94.95	104.82	64.32	:	THR	N	346	95.76	95.76	66.35
THR	CA	346	96.10	103.90	66.61	:	THR	CB	346	97.42	97.42	67.38
THR	OG1	346	98.36	104.17	66.29	:	THR	CG2	346	97.79	97.79	68.36
THR	C	346	95.00	103.10	67.24	:	THR	O	346	94.21	94.21	68.08
GLN	N	347	95.06	101.89	66.71	:	GLN	CA	347	94.06	94.06	66.83
GLN	CB	347	93.36	100.81	68.23	:	GLN	CG	347	94.14	94.14	69.53
GLN	CD	347	93.59	101.13	70.82	:	GLN	OE1	347	92.98	92.98	71.70

FIGURE 1 (cont.)

GLN	NE2	347	93.74	102.45	70.99	: GLN	E21	347	94.13	94.13	70.26
GLN	E22	347	93.42	102.81	71.84	: GLN	C	347	93.08	93.08	65.71
GLN	O	347	93.30	102.25	64.86	: GLY	N	348	91.97	91.97	65.72
GLY	CA	348	91.02	100.57	64.64	: GLY	C	348	89.86	89.86	64.81
GLY	O	348	89.64	99.04	65.89	: VAL	N	349	89.07	89.07	63.75
VAL	CA	349	87.98	98.51	63.71	: VAL	CB	349	86.71	86.71	64.44
VAL	CG1	349	86.21	100.36	63.82	: VAL	CG2	349	85.64	85.64	64.40
VAL	C	349	87.74	98.29	62.23	: VAL	O	349	87.99	87.99	61.46
LYS	N	350	87.40	97.10	61.76	: LYS	CA	350	87.10	87.10	60.35
LYS	CB	350	86.83	95.47	60.04	: LYS	CG	350	86.64	86.64	58.55
LYS	CD	350	86.41	93.72	58.35	: LYS	CE	350	85.88	85.88	56.95
LYS	NZ	350	86.88	93.73	55.94	: LYS	C	350	85.86	85.86	60.02
LYS	O	350	84.88	97.75	60.77	: GLY	N	351	85.89	85.89	58.88
GLY	CA	351	84.79	99.26	58.46	: GLY	C	351	84.81	84.81	56.95
GLY	O	351	85.69	98.65	56.35	: TRP	N	352	83.98	83.98	56.29
TRP	CA	352	83.73	100.13	54.87	: TRP	CB	352	82.59	82.59	54.50
TRP	CG	352	81.20	99.43	55.11	: TRP	CD2	352	80.21	80.21	54.52
TRP	CE2	352	79.31	100.37	55.56	: TRP	CE3	352	79.99	79.99	53.29
TRP	CD1	352	80.88	99.11	56.42	: TRP	NE1	352	79.73	79.73	56.65
TRP	CZ2	352	78.17	101.14	55.36	: TRP	CZ3	352	78.86	78.86	53.10
TRP	CH2	352	77.95	101.71	54.12	: TRP	C	352	83.28	83.28	54.54
TRP	O	352	82.95	102.37	55.43	: ALA	N	353	83.22	83.22	53.23
ALA	CA	353	82.68	103.11	52.69	: ALA	CB	353	83.59	83.59	52.98
ALA	C	353	82.64	102.89	51.19	: ALA	O	353	83.24	83.24	50.72
PHE	N	354	81.92	103.60	50.35	: PHE	CA	354	82.04	82.04	48.92
PHE	CB	354	81.10	102.43	48.31	: PHE	CG	354	79.59	79.59	48.41
PHE	CD1	354	78.95	102.28	49.60	: PHE	CD2	354	78.86	78.86	47.29
PHE	CE1	354	77.58	102.35	49.66	: PHE	CE2	354	77.49	77.49	47.37
PHE	CZ	354	76.86	102.73	48.55	: PHE	C	354	81.67	81.67	48.34
PHE	O	354	80.91	105.62	48.91	: ASP	N	355	82.28	82.28	47.21
ASP	CA	355	82.14	106.34	46.54	: ASP	CB	355	83.38	83.38	45.68
ASP	CG	355	83.37	105.68	44.43	: ASP	OD1	355	82.96	82.96	43.38
ASP	OD2	355	83.75	104.52	44.51	: ASP	C	355	80.87	80.87	45.71
ASP	O	355	80.31	105.29	45.38	: ASN	N	356	80.43	80.43	45.31
ASN	CA	356	79.28	107.70	44.45	: ASN	CB	356	77.97	77.97	45.26
ASN	CG	356	76.75	108.03	44.44	: ASN	OD1	356	76.05	76.05	44.80
ASN	ND2	356	76.42	107.41	43.31	: ASN	D21	356	76.93	76.93	42.91
ASN	D22	356	75.55	107.74	42.97	: ASN	C	356	79.52	79.52	43.91
ASN	O	356	79.25	110.11	44.57	: GLY	N	357	80.07	80.07	42.70
GLY	CA	357	80.49	110.43	42.11	: GLY	C	357	81.50	81.50	43.05
GLY	O	357	82.52	110.51	43.42	: ASN	N	358	81.15	81.15	43.61
ASN	CA	358	82.13	112.89	44.47	: ASN	CB	358	82.22	82.22	44.23
ASN	CG	358	82.66	114.74	42.80	: ASN	OD1	358	83.84	83.84	42.45
ASN	ND2	358	81.78	114.96	41.84	: ASN	D21	358	80.81	80.81	42.03
ASN	D22	358	82.16	115.17	40.96	: ASN	C	358	81.68	81.68	45.89
ASN	O	358	82.32	113.15	46.84	: ASP	N	359	80.63	80.63	46.12
ASP	CA	359	80.10	111.66	47.47	: ASP	CB	359	78.58	78.58	47.47
ASP	CG	359	78.13	113.04	46.75	: ASP	OD1	359	77.44	77.44	45.75
ASP	OD2	359	78.47	114.14	47.18	: ASP	C	359	80.49	80.49	48.02
ASP	O	359	80.93	109.41	47.31	: LEU	N	360	80.31	80.31	49.31
LEU	CA	360	80.75	109.10	50.04	: LEU	CB	360	81.89	81.89	50.97
LEU	CG	360	82.55	108.26	51.60	: LEU	CD1	360	83.53	83.53	50.56
LEU	CD2	360	83.11	108.62	52.96	: LEU	C	360	79.63	79.63	50.90
LEU	O	360	79.10	109.29	51.72	: TRP	N	361	79.31	79.31	50.74
TRP	CA	361	78.39	106.58	51.66	: TRP	CB	361	77.58	77.58	50.91
TRP	CG	361	76.38	106.17	50.24	: TRP	CD2	361	75.23	75.23	50.89
TRP	CE2	361	74.46	107.00	49.84	: TRP	CE3	361	74.73	74.73	52.16
TRP	CD1	361	76.35	106.40	48.88	: TRP	NE1	361	75.16	75.16	48.69

FIGURE 1 (cont.)

TRP	CZ2	361	73.18	107.50	50.06	:	TRP	CZ3	361	73.45	73.45	52.38
TRP	CH2	361	72.67	107.50	51.34	:	TRP	C	361	79.24	79.24	52.71
TRP	O	361	80.24	105.26	52.32	:	MET	N	362	78.95	78.95	54.00
MET	CA	362	79.85	105.21	54.93	:	MET	CB	362	81.05	81.05	55.26
MET	CG	362	80.71	107.51	55.72	:	MET	SD	362	82.15	82.15	56.38
MET	CE	362	82.08	108.03	58.13	:	MET	C	362	79.15	79.15	56.21
MET	O	362	78.03	105.33	56.42	:	GLY	N	363	79.77	79.77	57.07
GLY	CA	363	79.19	103.80	58.35	:	GLY	C	363	80.28	80.28	59.36
GLY	O	363	81.45	103.99	58.99	:	ARG	N	364	79.99	79.99	60.63
ARG	CA	364	81.02	103.97	61.64	:	ARG	CB	364	81.69	81.69	61.82
ARG	CG	364	81.00	106.63	61.31	:	ARG	CD	364	81.42	81.42	62.22
ARG	NE	364	81.50	109.05	61.55	:	ARG	CZ	364	81.04	81.04	62.09
ARG	NH1	364	81.18	111.30	61.39	:	ARG	NH2	364	80.48	80.48	63.30
ARG	C	364	80.31	103.68	62.93	:	ARG	O	364	79.08	79.08	62.93
THR	N	365	81.02	103.50	64.03	:	THR	CA	365	80.32	80.32	65.27
THR	CB	365	81.29	102.68	66.29	:	THR	OG1	365	82.46	82.46	66.49
THR	CG2	365	81.77	101.34	65.73	:	THR	C	365	79.82	79.82	65.67
THR	O	365	80.33	105.72	65.19	:	ILE	N	366	78.77	78.77	66.45
ILE	CA	366	78.30	106.14	66.83	:	ILE	CB	366	76.85	76.85	67.39
ILE	CG2	366	76.43	107.26	68.20	:	ILE	CG1	366	75.95	75.95	66.17
ILE	CD1	366	74.50	105.42	66.44	:	ILE	C	366	79.30	79.30	67.84
ILE	O	366	79.66	107.82	67.79	:	SER	N	367	79.79	79.79	68.74
SER	CA	367	80.83	106.21	69.66	:	SER	CB	367	81.07	81.07	70.66
SER	OG	367	81.90	105.41	71.77	:	SER	C	367	82.12	82.12	68.87
SER	O	367	82.28	106.05	67.72	:	LYS	N	368	83.07	83.07	69.43
LYS	CA	368	84.38	107.39	68.78	:	LYS	CB	368	84.64	84.64	68.58
LYS	CG	368	84.69	109.61	69.92	:	LYS	CD	368	84.78	84.78	69.83
LYS	CE	368	84.73	111.66	71.26	:	LYS	NZ	368	85.82	85.82	72.07
LYS	C	368	85.46	106.76	69.65	:	LYS	O	368	86.63	86.63	69.30
ASP	N	369	85.05	106.19	70.78	:	ASP	CA	369	85.96	85.96	71.72
ASP	CB	369	85.71	106.18	73.10	:	ASP	CG	369	85.83	85.83	73.18
ASP	OD1	369	86.63	108.28	72.46	:	ASP	OD2	369	85.10	85.10	73.97
ASP	C	369	85.77	104.10	71.76	:	ASP	O	369	86.73	86.73	71.70
LEU	N	370	84.52	103.69	71.87	:	LEU	CA	370	84.13	84.13	71.95
LEU	CB	370	83.14	102.19	73.06	:	LEU	CG	370	83.62	83.62	74.40
LEU	CD1	370	85.07	102.06	74.71	:	LEU	CD2	370	82.63	82.63	75.39
LEU	C	370	83.49	101.91	70.64	:	LEU	O	370	83.04	83.04	69.89
ARG	N	371	83.38	100.63	70.32	:	ARG	CA	371	82.62	82.62	69.11
ARG	CB	371	83.27	99.20	68.28	:	ARG	CG	371	84.10	84.10	68.94
ARG	CD	371	85.33	98.06	68.06	:	ARG	NE	371	85.96	85.96	68.38
ARG	CZ	371	87.02	96.29	67.76	:	ARG	NH1	371	87.41	87.41	68.14
ARG	NH2	371	87.72	96.93	66.82	:	ARG	C	371	81.20	81.20	69.49
ARG	O	371	80.84	98.77	69.73	:	SER	N	372	80.43	80.43	69.63
SER	CA	372	79.02	100.98	70.02	:	SER	CB	372	78.85	78.85	71.38
SER	OG	372	79.63	100.86	72.34	:	SER	C	372	78.24	78.24	69.02
SER	O	372	78.77	102.79	68.45	:	GLY	N	373	76.99	76.99	68.81
GLY	CA	373	76.08	102.02	67.89	:	GLY	C	373	76.57	76.57	66.47
GLY	O	373	77.74	101.51	66.27	:	TYR	N	374	75.80	75.80	65.44
TYR	CA	374	76.36	102.16	64.13	:	TYR	CB	374	76.33	76.33	63.57
TYR	CG	374	77.25	100.60	62.38	:	TYR	CD1	374	76.74	76.74	61.08
TYR	CE1	374	77.61	100.63	60.01	:	TYR	CD2	374	78.61	78.61	62.59
TYR	CE2	374	79.49	100.23	61.52	:	TYR	CZ	374	78.97	78.97	60.25
TYR	OH	374	79.84	100.29	59.17	:	TYR	C	374	75.44	75.44	63.38
TYR	O	374	74.23	103.06	63.60	:	GLU	N	375	75.97	75.97	62.52
GLU	CA	375	75.19	104.95	61.82	:	GLU	CB	375	75.47	75.47	62.50
GLU	CG	375	76.74	107.19	62.21	:	GLU	CD	375	77.25	77.25	63.38
GLU	OE1	375	76.52	108.49	64.27	:	GLU	OE2	375	78.45	78.45	63.44
GLU	C	375	75.64	104.91	60.37	:	GLU	O	375	76.76	76.76	60.13

THR	N	376	74.85	105.28	59.37	: THR	CA	376	75.33	75.33	58.00
THR	CB	376	74.74	104.36	57.01	: THR	OG1	376	73.32	73.32	57.13
THR	CG2	376	75.23	103.00	57.33	: THR	C	376	74.91	74.91	57.52
THR	O	376	73.97	107.42	58.10	: PHE	N	377	75.56	75.56	56.52
PHE	CA	377	75.16	108.70	55.94	: PHE	CB	377	75.47	75.47	56.88
PHE	CG	377	76.79	109.89	57.66	: PHE	CD1	377	76.78	76.78	58.99
PHE	CD2	377	77.97	110.29	57.05	: PHE	CE1	377	77.94	77.94	59.73
PHE	CE2	377	79.12	110.32	57.80	: PHE	CZ	377	79.11	79.11	59.13
PHE	C	377	75.90	108.93	54.65	: PHE	O	377	76.83	76.83	54.36
LYS	N	378	75.44	109.87	53.81	: LYS	CA	378	76.17	76.17	52.62
LYS	CB	378	75.25	110.71	51.49	: LYS	CG	378	75.77	75.77	50.06
LYS	CD	378	74.73	111.51	49.29	: LYS	CE	378	74.19	74.19	47.91
LYS	NZ	378	75.16	111.19	46.81	: LYS	C	378	76.97	76.97	53.08
LYS	O	378	76.61	112.20	54.06	: VAL	N	379	78.13	78.13	52.50
VAL	CA	379	78.92	112.97	52.77	: VAL	CB	379	80.31	80.31	53.35
VAL	CG1	379	80.95	114.00	53.73	: VAL	CG2	379	80.25	80.25	54.63
VAL	C	379	79.06	113.59	51.39	: VAL	O	379	79.53	79.53	50.42
ILE	N	380	78.52	114.82	51.28	: ILE	CA	380	78.62	78.62	50.02
ILE	CB	380	77.63	116.70	49.97	: ILE	CG2	380	77.58	77.58	48.52
ILE	CG1	380	76.20	116.36	50.32	: ILE	CD1	380	75.80	75.80	51.79
ILE	C	380	80.07	116.01	49.93	: ILE	O	380	80.73	80.73	50.91
GLY	N	381	80.58	115.71	48.74	: GLY	CA	381	81.99	81.99	48.44
GLY	C	381	82.92	114.92	49.13	: GLY	O	381	84.08	84.08	48.74
GLY	N	382	82.34	114.05	49.98	: GLY	CA	382	83.04	83.04	50.85
GLY	C	382	84.11	112.31	50.18	: GLY	O	382	85.04	85.04	50.87
TRP	N	383	83.97	112.08	48.88	: TRP	CA	383	84.94	84.94	48.17
TRP	CB	383	84.35	110.52	46.96	: TRP	CG	383	85.39	85.39	46.25
TRP	CD2	383	86.15	108.63	46.79	: TRP	CE2	383	86.95	86.95	45.70
TRP	CE3	383	86.29	107.95	48.00	: TRP	CD1	383	85.69	85.69	44.93
TRP	NE1	383	86.64	109.06	44.63	: TRP	CZ2	383	87.88	87.88	45.83
TRP	CZ3	383	87.21	106.91	48.11	: TRP	CH2	383	88.01	88.01	47.04
TRP	C	383	86.04	112.19	47.66	: TRP	O	383	87.21	87.21	47.97
SER	N	384	85.68	113.18	46.83	: SER	CA	384	86.63	86.63	46.21
SER	CB	384	86.07	114.49	44.88	: SER	OG	384	86.07	86.07	44.02
SER	C	384	87.07	115.35	46.94	: SER	O	384	87.95	87.95	46.40
THR	N	385	86.61	115.79	48.10	: THR	CA	385	87.15	87.15	48.53
THR	CB	385	86.05	118.17	48.41	: THR	OG1	385	85.19	85.19	49.52
THR	CG2	385	85.18	118.02	47.17	: THR	C	385	87.73	87.73	49.91
THR	O	385	87.15	116.37	50.84	: PRO	N	386	88.97	88.97	50.03
PRO	CD	386	89.78	117.94	48.94	: PRO	CA	386	89.70	89.70	51.27
PRO	CB	386	90.94	118.06	51.03	: PRO	CG	386	91.15	91.15	49.53
PRO	C	386	88.85	117.76	52.40	: PRO	O	386	88.24	88.24	52.26
ASN	N	387	88.69	117.01	53.47	: ASN	CA	387	88.00	88.00	54.68
ASN	CB	387	88.83	118.51	55.25	: ASN	CG	387	88.92	88.92	56.75
ASN	OD1	387	89.24	119.37	57.42	: ASN	ND2	387	88.83	88.83	57.45
ASN	D21	387	88.81	116.43	56.97	: ASN	D22	387	88.67	88.67	58.42
ASN	C	387	86.51	117.80	54.68	: ASN	O	387	86.00	86.00	55.70
SER	N	388	85.75	117.52	53.61	: SER	CA	388	84.31	84.31	53.57
SER	CB	388	83.71	117.10	52.32	: SER	OG	388	84.46	84.46	51.73
SER	C	388	83.63	117.08	54.76	: SER	O	388	83.85	83.85	55.01
LYS	N	389	82.90	117.85	55.58	: LYS	CA	389	82.18	82.18	56.71
LYS	CB	389	82.68	117.90	58.02	: LYS	CG	389	84.16	84.16	58.24
LYS	CD	389	84.32	118.29	59.71	: LYS	CE	389	85.79	85.79	59.95
LYS	NZ	389	86.11	118.14	61.32	: LYS	C	389	80.67	80.67	56.62
LYS	O	389	80.02	117.61	57.66	: SER	N	390	80.09	80.09	55.42
SER	CA	39	78.67	117.99	55.30	: SER	CB	390	78.35	78.35	53.82
SER	OG	390	78.64	116.87	53.15	: SER	C	390	77.67	77.67	55.94
SER	O	390	77.18	117.31	57.06	: GLN	N	391	77.35	77.35	55.26

FIGURE 1 (cont.)

GLN	CA	391	76.43	114.84	55.68	:	GLN	CB	391	76.59	76.59	57.18
GLN	CG	391	75.64	113.54	57.66	:	GLN	CD	391	75.70	75.70	59.12
GLN	OE1	391	74.72	112.75	59.66	:	GLN	NE2	391	76.76	76.76	59.85
GLN	E21	391	77.54	114.01	59.46	:	GLN	E22	391	76.71	76.71	60.81
GLN	C	391	74.95	115.08	55.40	:	GLN	O	391	74.41	74.41	55.61
ILE	N	392	74.29	114.05	54.90	:	ILE	CA	392	72.85	72.85	54.68
ILE	CB	392	72.52	114.62	53.33	:	ILE	CG2	392	73.02	73.02	52.19
ILE	CG1	392	71.01	114.79	53.24	:	ILE	CD1	392	70.57	70.57	52.28
ILE	C	392	72.47	112.50	54.71	:	ILE	O	392	73.37	73.37	54.62
ASN	N	393	71.18	112.15	54.85	:	ASN	CA	393	70.64	70.64	54.82
ASN	CB	393	70.87	110.13	53.50	:	ASN	CG	393	70.18	70.18	52.35
ASN	OD1	393	70.64	110.80	51.20	:	ASN	ND2	393	69.06	69.06	52.53
ASN	D21	393	68.67	111.60	53.42	:	ASN	D22	393	68.69	68.69	51.71
ASN	C	393	71.24	109.93	55.89	:	ASN	O	393	71.64	71.64	55.67
ARG	N	394	71.37	110.48	57.09	:	ARG	CA	394	71.85	71.85	58.15
ARG	CB	394	72.17	110.54	59.31	:	ARG	CG	394	72.18	72.18	60.61
ARG	CD	394	73.20	110.11	61.60	:	ARG	NE	394	72.44	72.44	62.83
ARG	CZ	394	72.83	109.56	63.94	:	ARG	NH1	394	72.11	72.11	65.06
ARG	NH2	394	73.91	108.82	63.97	:	ARG	C	394	70.81	70.81	58.48
ARG	O	394	69.62	108.80	58.23	:	GLN	N	395	71.23	71.23	59.01
GLN	CA	395	70.37	106.29	59.48	:	GLN	CB	395	70.23	70.23	58.51
GLN	CG	395	69.53	105.60	57.26	:	GLN	CD	395	69.29	69.29	56.26
GLN	OE1	395	69.65	104.60	55.09	:	GLN	NE2	395	68.65	68.65	56.61
GLN	E21	395	68.43	103.31	57.55	:	GLN	E22	395	68.38	68.38	55.91
GLN	C	395	71.03	105.71	60.68	:	GLN	O	395	72.25	72.25	60.67
VAL	N	396	70.32	105.37	61.74	:	VAL	CA	396	70.88	70.88	62.84
VAL	CB	396	70.22	105.08	64.12	:	VAL	CG1	396	70.47	70.47	65.25
VAL	CG2	396	70.80	106.39	64.50	:	VAL	C	396	70.56	70.56	62.51
VAL	O	396	69.48	102.80	62.05	:	ILE	N	397	71.57	71.57	62.59
ILE	CA	397	71.38	100.87	62.38	:	ILE	CB	397	72.51	72.51	61.49
ILE	CG2	397	72.29	98.83	61.28	:	ILE	CG1	397	72.59	72.59	60.18
ILE	CD1	397	71.39	101.19	59.21	:	ILE	C	397	71.40	71.40	63.79
ILE	O	397	70.58	99.40	64.10	:	VAL	N	398	72.25	72.25	64.71
VAL	CA	398	72.29	100.11	66.06	:	VAL	CB	398	73.53	73.53	66.33
VAL	CG1	398	73.49	98.62	67.77	:	VAL	CG2	398	73.52	73.52	65.38
VAL	C	398	72.42	101.36	66.92	:	VAL	O	398	73.28	73.28	66.65
ASP	N	399	71.54	101.56	67.89	:	ASP	CA	399	71.61	71.61	68.73
ASP	CB	399	70.35	102.82	69.58	:	ASP	CG	399	70.17	70.17	70.54
ASP	OD1	399	70.66	101.71	71.67	:	ASP	OD2	399	69.54	69.54	70.14
ASP	C	399	72.84	102.73	69.61	:	ASP	O	399	73.37	73.37	69.96
SER	N	400	73.20	103.92	70.07	:	SER	CA	400	74.37	74.37	70.87
SER	CB	400	74.41	105.68	71.18	:	SER	OG	400	73.13	73.13	71.64
SER	C	400	74.46	103.43	72.16	:	SER	O	400	75.51	75.51	72.81
ASP	N	401	73.36	102.86	72.60	:	ASP	CA	401	73.48	73.48	73.82
ASP	CB	401	72.21	102.33	74.63	:	ASP	CG	401	72.49	72.49	75.43
ASP	OD1	401	72.78	103.46	76.63	:	ASP	OD2	401	72.48	72.48	74.86
ASP	C	401	73.78	100.65	73.64	:	ASP	O	401	73.94	73.94	74.60
ASN	N	402	73.93	100.25	72.39	:	ASN	CA	402	74.18	74.18	72.10
ASN	CB	402	73.06	98.29	71.29	:	ASN	CG	402	71.86	71.86	72.16
ASN	OD1	402	71.80	97.11	73.00	:	ASN	ND2	402	70.78	70.78	71.93
ASN	D21	402	70.80	99.36	71.20	:	ASN	D22	402	70.04	70.04	72.55
ASN	C	402	75.47	98.72	71.33	:	ASN	O	402	75.91	75.91	70.59
ARG	N	403	76.01	97.53	71.47	:	ARG	CA	403	77.29	77.29	70.88
ARG	CB	403	77.78	95.92	71.50	:	ARG	CG	403	77.86	77.86	73.00
ARG	CD	403	79.29	95.62	73.18	:	ARG	NE	403	79.50	79.50	74.11
ARG	CZ	403	80.63	93.83	74.02	:	ARG	NH1	403	80.83	80.83	74.92
ARG	NH2	403	81.55	94.00	73.07	:	ARG	C	403	77.24	77.24	69.40
ARG	O	403	76.21	96.40	68.89	:	SER	N	404	78.32	78.32	68.69

FIGURE 1 (cont.)

SER	CA	404	78.48	96.79	67.32	: SER	CB	404	78.40	78.40	66.37
SER	OG	404	79.29	98.93	66.88	: SER	C	404	79.85	79.85	67.22
SER	O	404	80.25	95.37	68.17	: GLY	N	405	80.68	80.68	66.20
GLY	CA	405	81.99	95.57	66.09	: GLY	C	405	82.37	82.37	64.66
GLY	O	405	82.16	96.99	64.18	: TYR	N	406	82.91	82.91	63.98
TYR	CA	406	83.36	94.99	62.61	: TYR	CB	406	84.08	84.08	62.21
TYR	CG	406	85.50	93.54	62.73	: TYR	CD1	406	86.41	86.41	62.02
TYR	CE1	406	87.72	92.67	62.44	: TYR	CD2	406	85.91	85.91	63.86
TYR	CE2	406	87.21	94.12	64.28	: TYR	CZ	406	88.11	88.11	63.57
TYR	OH	406	89.42	93.29	64.00	: TYR	C	406	82.27	82.27	61.62
TYR	O	406	81.13	94.98	61.94	: SER	N	407	82.53	82.53	60.41
SER	CA	407	81.51	95.85	59.43	: SER	CB	407	80.85	80.85	59.51
SER	OG	407	81.73	98.36	59.63	: SER	C	407	82.23	82.23	58.12
SER	O	407	83.44	95.88	58.08	: GLY	N	408	81.56	81.56	57.03
GLY	CA	408	82.27	95.36	55.80	: GLY	C	408	81.19	81.19	54.77
GLY	O	408	80.00	95.21	55.06	: ILE	N	409	81.61	81.61	53.53
ILE	CA	409	80.70	95.76	52.44	: ILE	CB	409	81.31	81.31	51.61
ILE	CG2	409	82.45	96.36	50.76	: ILE	CG1	409	80.26	80.26	50.75
ILE	CD1	409	80.74	98.67	49.80	: ILE	C	409	80.54	80.54	51.67
ILE	O	409	81.41	93.57	51.80	: PHE	N	410	79.46	79.46	50.90
PHE	CA	410	79.40	93.20	49.95	: PHE	CB	410	78.82	78.82	50.60
PHE	CG	410	77.38	91.82	51.06	: PHE	CD1	410	77.06	77.06	52.35
PHE	CD2	410	76.42	91.34	50.20	: PHE	CE1	410	75.76	75.76	52.78
PHE	CE2	410	75.11	91.18	50.63	: PHE	CZ	410	74.79	74.79	51.92
PHE	C	410	78.56	93.70	48.80	: PHE	O	410	77.76	77.76	48.97
SER	N	411	78.69	93.12	47.64	: SER	CA	411	78.04	78.04	46.47
SER	CB	411	79.08	94.04	45.44	: SER	OG	411	79.93	79.93	45.90
SER	C	411	77.13	92.58	45.85	: SER	O	411	77.56	77.56	45.78
VAL	N	412	75.89	92.88	45.42	: VAL	CA	412	75.10	75.10	44.74
VAL	CB	412	73.82	91.48	45.62	: VAL	CG1	412	74.13	74.13	47.13
VAL	CG2	412	72.65	92.40	45.30	: VAL	C	412	74.73	74.73	43.34
VAL	O	412	74.34	93.53	43.11	: GLU	N	413	74.99	74.99	42.35
GLU	CA	413	74.65	91.88	40.97	: GLU	CB	413	75.09	75.09	40.12
GLU	CG	413	75.99	90.95	38.93	: GLU	CD	413	75.27	75.27	37.69
GLU	OE1	413	74.40	92.30	37.85	: GLU	OE2	413	75.58	75.58	36.58
GLU	C	413	73.13	92.06	40.88	: GLU	O	413	72.41	72.41	41.50
GLY	N	414	72.56	93.06	40.21	: GLY	CA	414	71.11	71.11	40.10
GLY	C	414	70.80	93.18	38.62	: GLY	O	414	71.73	71.73	37.82
LYS	N	415	69.54	93.26	38.15	: LYS	CA	415	69.25	69.25	36.71
LYS	CB	415	67.76	93.34	36.51	: LYS	CG	415	67.19	67.19	35.57
LYS	CD	415	65.70	92.50	35.18	: LYS	CE	415	64.72	64.72	36.38
LYS	NZ	415	64.57	91.16	36.94	: LYS	C	415	69.94	69.94	35.88
LYS	O	415	70.44	94.15	34.76	: SER	N	416	69.91	69.91	36.55
SER	CA	416	70.24	96.74	36.09	: SER	CB	416	69.14	69.14	36.69
SER	OG	416	68.81	97.04	37.99	: SER	C	416	71.63	71.63	36.41
SER	O	416	72.38	97.82	35.60	: CYS	N	417	71.91	71.91	37.68
CYS	CA	417	73.07	97.77	38.27	: CYS	C	417	73.64	73.64	39.37
CYS	O	417	72.94	95.90	39.75	: CYS	CB	417	72.60	72.60	38.84
CYS	SG	417	71.28	98.82	40.04	: ILE	N	418	74.85	74.85	39.92
ILE	CA	418	75.24	96.25	41.05	: ILE	CB	418	76.71	76.71	40.89
ILE	CG2	418	76.97	95.19	39.43	: ILE	CG1	418	77.79	77.79	41.39
ILE	CD1	418	78.39	95.65	42.54	: ILE	C	418	75.12	75.12	42.27
ILE	O	418	75.43	98.37	42.26	: ASN	N	419	74.50	74.50	43.29
ASN	CA	419	74.17	97.30	44.52	: ASN	CB	419	72.75	72.75	44.92
ASN	CG	419	72.18	97.51	46.17	: ASN	OD1	419	71.53	71.53	46.97
ASN	ND2	419	72.42	98.78	46.47	: ASN	D21	419	72.96	72.96	45.87
ASN	D22	419	71.97	99.14	47.26	: ASN	C	419	75.20	75.20	45.59
ASN	O	419	75.99	96.05	45.38	: ARG	N	420	75.19	75.19	46.76

FIGURE 1 (cont.)

ARG	CA	420	76.21	97.50	47.76	: ARG	CB	420	77.02	77.02	48.01
ARG	CG	420	77.61	99.45	46.79	: ARG	CD	420	78.79	78.79	46.33
ARG	NE	420	79.24	99.29	45.11	: ARG	CZ	420	80.01	80.01	44.21
ARG	NH1	420	80.30	99.42	43.14	: ARG	NH2	420	80.50	80.50	44.31
ARG	C	420	75.42	97.29	49.00	: ARG	O	420	74.44	74.44	49.24
CYS	N	421	75.87	96.40	49.85	: CYS	CA	421	75.12	75.12	51.05
CYS	C	421	76.19	95.98	52.11	: CYS	O	421	77.37	77.37	51.78
CYS	CB	421	74.38	94.74	50.83	: CYS	SG	421	73.31	73.31	49.39
PHE	N	422	75.93	95.84	53.39	: PHE	CA	422	76.97	76.97	54.38
PHE	CB	422	77.28	97.26	54.82	: PHE	CG	422	76.27	76.27	55.68
PHE	CD1	422	76.32	97.88	57.07	: PHE	CD2	422	75.32	75.32	55.09
PHE	CE1	422	75.43	98.58	57.87	: PHE	CE2	422	74.44	74.44	55.90
PHE	CZ	422	74.48	99.42	57.28	: PHE	C	422	76.46	76.46	55.56
PHE	O	422	75.25	94.98	55.82	: TYR	N	423	77.30	77.30	56.35
TYR	CA	423	76.82	93.63	57.56	: TYR	CB	423	77.39	77.39	57.68
TYR	CG	423	78.94	92.12	57.56	: TYR	CD1	423	79.54	79.54	56.31
TYR	CE1	423	80.91	92.04	56.21	: TYR	CD2	423	79.74	79.74	58.71
TYR	CE2	423	81.13	92.20	58.61	: TYR	CZ	423	81.68	81.68	57.35
TYR	OH	423	83.03	92.16	57.16	: TYR	C	423	77.35	77.35	58.72
TYR	O	423	78.33	95.13	58.53	: VAL	N	424	76.84	76.84	59.92
VAL	CA	424	77.61	94.74	61.04	: VAL	CB	424	77.20	77.20	61.57
VAL	CG1	424	75.98	96.79	60.90	: VAL	CG2	424	77.05	77.05	63.05
VAL	C	424	77.47	93.69	62.11	: VAL	O	424	76.41	76.41	62.37
GLU	N	425	78.65	93.37	62.62	: GLU	CA	425	78.87	78.87	63.66
GLU	CB	425	80.33	92.01	63.63	: GLU	CG	425	80.81	80.81	64.91
GLU	CD	425	82.28	90.98	64.89	: GLU	OE1	425	83.11	83.11	64.48
GLU	OE2	425	82.61	89.88	65.32	: GLU	C	425	78.52	78.52	64.96
GLU	O	425	78.91	94.22	65.14	: LEU	N	426	77.88	77.88	65.88
LEU	CA	426	77.43	92.90	67.17	: LEU	CB	426	75.90	75.90	67.27
LEU	CG	426	75.14	93.13	65.97	: LEU	CD1	426	73.68	73.68	66.10
LEU	CD2	426	75.29	94.62	65.65	: LEU	C	426	78.07	78.07	68.16
LEU	O	426	77.57	90.84	68.37	: ILE	N	427	79.21	79.21	68.72
ILE	CA	427	79.91	91.42	69.55	: ILE	CB	427	81.56	81.56	69.38
ILE	CG2	427	82.01	92.58	68.38	: ILE	CG1	427	82.19	82.19	70.64
ILE	CD1	427	82.57	90.67	71.37	: ILE	C	427	79.36	79.36	70.97
ILE	O	427	78.78	92.59	71.35	: ARG	N	428	79.40	79.40	71.70
ARG	CA	428	78.87	90.35	73.04	: ARG	CB	428	77.56	77.56	73.10
ARG	CG	428	76.46	90.26	72.33	: ARG	CD	428	76.21	76.21	72.98
ARG	NE	428	74.81	91.62	73.24	: ARG	CZ	428	74.26	74.26	74.44
ARG	NH1	428	72.97	91.52	74.48	: ARG	NH2	428	74.91	74.91	75.59
ARG	C	428	79.85	89.53	73.82	: ARG	O	428	80.52	80.52	73.28
GLY	N	429	79.77	89.76	75.12	: GLY	CA	429	80.62	80.62	76.03
GLY	C	429	81.89	89.80	76.38	: GLY	O	429	82.01	82.01	76.31
ARG	N	430	82.82	88.96	76.80	: ARG	CA	430	84.03	84.03	77.38
ARG	CB	430	84.73	88.22	78.05	: ARG	CG	430	84.56	84.56	79.57
ARG	CD	430	85.49	87.48	80.32	: ARG	NE	430	85.76	85.76	81.73
ARG	CZ	430	84.87	87.64	82.72	: ARG	NH1	430	85.23	85.23	83.99
ARG	NH2	430	83.60	87.33	82.50	: ARG	C	430	85.01	85.01	76.55
ARG	O	430	85.00	90.51	75.35	: LYS	N	431	85.36	85.36	77.64
LYS	CA	431	86.27	92.03	77.86	: LYS	CB	431	87.02	87.02	76.59
LYS	CG	431	88.52	92.55	76.96	: LYS	CD	431	88.99	88.99	77.94
LYS	CE	431	90.47	91.56	78.24	: LYS	NZ	431	91.23	91.23	77.11
LYS	C	431	85.22	93.02	78.29	: LYS	O	431	85.02	85.02	79.50
GLN	N	432	84.43	93.64	77.41	: GLN	CA	432	83.44	83.44	77.87
GLN	CB	432	82.81	95.29	76.68	: GLN	CG	432	81.71	81.71	77.09
GLN	CD	432	81.29	97.28	76.03	: GLN	OE1	432	81.93	81.93	74.98
GLN	NE2	432	80.24	98.05	76.30	: GLN	E21	432	79.81	79.81	77.18
GLN	E22	432	79.94	98.65	75.58	: GLN	C	432	82.35	82.35	78.76

FIGURE 1 (cont.)

GLN	O	432	82.14	94.52	79.85	: GLU	N	433	81.62	81.62	78.36
GLU	CA	433	80.59	92.37	79.21	: GLU	CB	433	79.47	79.47	78.38
GLU	CG	433	78.90	93.03	77.70	: GLU	CD	433	77.70	77.70	76.84
GLU	OE1	433	77.85	92.17	75.76	: GLU	OE2	433	76.61	76.61	77.27
GLU	C	433	81.24	91.27	79.99	: GLU	O	433	82.01	82.01	79.46
THR	N	434	80.90	91.16	81.26	: THR	CA	434	81.66	81.66	82.20
THR	CB	434	82.43	91.51	82.94	: THR	OG1	434	83.73	83.73	82.38
THR	CG2	434	82.40	91.50	84.46	: THR	C	434	80.88	80.88	83.04
THR	O	434	81.43	88.71	83.92	: ARG	N	435	79.57	79.57	82.86
ARG	CA	435	78.85	88.20	83.62	: ARG	CB	435	77.34	77.34	83.46
ARG	CG	435	76.70	87.64	84.63	: ARG	CD	435	75.21	75.21	84.61
ARG	NE	435	74.75	86.98	83.49	: ARG	CZ	435	74.49	74.49	83.56
ARG	NH1	435	74.13	85.04	82.47	: ARG	NH2	435	74.55	74.55	84.67
ARG	C	435	79.25	86.81	83.11	: ARG	O	435	79.53	79.53	83.86
VAL	N	436	79.41	86.81	81.78	: VAL	CA	436	79.73	79.73	80.99
VAL	CB	436	78.94	85.69	79.68	: VAL	CG1	436	77.46	77.46	80.04
VAL	CG2	436	79.32	86.91	78.82	: VAL	C	436	81.21	81.21	80.69
VAL	O	436	81.82	86.72	80.47	: TRP	N	437	81.79	81.79	80.54
TRP	CA	437	83.20	84.34	80.23	: TRP	CB	437	83.77	83.77	80.98
TRP	CG	437	83.87	83.56	82.43	: TRP	CD2	437	85.01	85.01	83.07
TRP	CE2	437	84.58	84.00	84.38	: TRP	CE3	437	86.30	86.30	82.72
TRP	CD1	437	82.80	83.39	83.26	: TRP	NE1	437	83.28	83.28	84.44
TRP	CZ2	437	85.46	84.36	85.39	: TRP	CZ3	437	87.17	87.17	83.72
TRP	CH2	437	86.75	84.68	85.04	: TRP	C	437	83.56	83.56	78.79
TRP	O	437	84.75	83.99	78.47	: TRP	N	438	82.59	82.59	77.88
TRP	CA	438	82.80	83.88	76.46	: TRP	CB	438	81.68	81.68	75.90
TRP	CG	438	80.26	83.41	76.28	: TRP	CD2	438	79.45	79.45	75.66
TRP	CE2	438	78.32	84.30	76.46	: TRP	CE3	438	79.51	79.51	74.56
TRP	CD1	438	79.68	82.86	77.37	: TRP	NE1	438	78.50	78.50	77.46
TRP	CZ2	438	77.22	85.09	76.19	: TRP	CZ3	438	78.42	78.42	74.30
TRP	CH2	438	77.29	85.93	75.10	: TRP	C	438	82.81	82.81	75.73
TRP	O	438	82.51	86.23	76.31	: THR	N	439	83.01	83.01	74.44
THR	CA	439	83.00	86.39	73.63	: THR	CB	439	84.45	84.45	73.39
THR	OG1	439	85.03	87.11	74.66	: THR	CG2	439	84.54	84.54	72.46
THR	C	439	82.38	85.82	72.35	: THR	O	439	82.88	82.88	71.92
SER	N	440	81.33	86.36	71.73	: SER	CA	440	80.83	80.83	70.45
SER	CB	440	79.87	84.68	70.70	: SER	OG	440	79.47	79.47	69.50
SER	C	440	80.11	87.03	69.76	: SER	O	440	80.07	80.07	70.31
ASN	N	441	79.51	86.90	68.59	: ASN	CA	441	78.79	78.79	67.97
ASN	CB	441	79.65	88.60	66.93	: ASN	CG	441	79.77	79.77	65.68
ASN	OD1	441	80.44	86.71	65.69	: ASN	ND2	441	79.17	79.17	64.54
ASN	D21	441	78.62	88.90	64.53	: ASN	D22	441	79.23	79.23	63.79
ASN	C	441	77.51	87.46	67.29	: ASN	O	441	77.34	77.34	67.15
SER	N	442	76.60	88.38	66.91	: SER	CA	442	75.53	75.53	65.98
SER	CB	442	74.18	88.18	66.64	: SER	OG	442	73.72	73.72	67.04
SER	C	442	75.67	89.00	64.81	: SER	O	442	76.65	76.65	64.74
ILE	N	443	74.83	89.01	63.79	: ILE	CA	443	75.00	75.00	62.70
ILE	CB	443	75.58	89.25	61.37	: ILE	CG2	443	76.71	76.71	61.74
ILE	CG1	443	74.69	88.27	60.67	: ILE	CD1	443	75.23	75.23	59.24
ILE	C	443	73.63	90.52	62.39	: ILE	O	443	72.57	72.57	62.70
VAL	N	444	73.67	91.68	61.72	: VAL	CA	444	72.52	72.52	61.15
VAL	CB	444	72.11	93.54	62.09	: VAL	CG1	444	73.07	73.07	62.12
VAL	CG2	444	70.78	94.01	61.59	: VAL	C	444	73.04	73.04	59.79
VAL	O	444	74.25	92.95	59.66	: VAL	N	445	72.30	72.30	58.70
VAL	CA	445	72.85	93.21	57.42	: VAL	CB	445	73.41	73.41	56.56
VAL	CG1	445	73.09	90.61	57.19	: VAL	CG2	445	72.89	72.89	55.16
VAL	C	445	71.76	93.99	56.74	: VAL	O	445	70.57	70.57	56.96
PHE	N	446	72.13	95.03	56.01	: PHE	CA	446	71.21	71.21	55.32

FIGURE 1 (cont.)

PHE	CB	446	71.26	97.32	55.91	: PHE	CG	446	70.42	70.42	57.17
PHE	CD1	446	69.45	98.48	57.18	: PHE	CD2	446	70.59	70.59	58.25
PHE	CE1	446	68.64	98.63	58.27	: PHE	CE2	446	69.78	69.78	59.35
PHE	CZ	446	68.82	97.79	59.35	: PHE	C	446	71.65	71.65	53.88
PHE	O	446	72.85	95.85	53.60	: CYS	N	447	70.76	70.76	52.92
CYS	CA	447	71.22	96.44	51.57	: CYS	C	447	70.85	70.85	51.13
CYS	O	447	70.05	98.49	51.78	: CYS	CB	447	70.66	70.66	50.56
CYS	SG	447	71.77	93.98	50.66	: GLY	N	448	71.49	71.49	50.06
GLY	CA	448	71.18	99.56	49.55	: GLY	C	448	69.82	69.82	48.89
GLY	O	448	69.39	98.50	48.29	: THR	N	449	69.10	69.10	49.09
THR	CA	449	67.84	100.72	48.43	: THR	CB	449	66.69	66.69	49.45
THR	OG1	449	65.56	100.89	48.62	: THR	CG2	449	66.68	66.68	50.56
THR	C	449	67.85	102.02	47.66	: THR	O	449	68.54	68.54	48.05
SER	N	450	67.05	102.07	46.60	: SER	CA	450	66.87	66.87	45.91
SER	CB	450	67.09	103.03	44.49	: SER	OG	450	65.94	65.94	43.97
SER	C	450	65.47	103.89	46.15	: SER	O	450	65.06	65.06	45.49
GLY	N	451	64.67	103.32	47.04	: GLY	CA	451	63.30	63.30	47.30
GLY	C	451	63.27	104.37	48.65	: GLY	O	451	64.26	64.26	49.00
THR	N	452	62.27	104.18	49.48	: THR	CA	452	62.12	62.12	50.73
THR	CB	452	60.72	105.57	50.86	: THR	OG1	452	59.99	59.99	49.62
THR	CG2	452	60.93	106.98	51.31	: THR	C	452	62.27	62.27	51.90
THR	O	452	62.17	102.82	51.71	: TYR	N	453	62.36	62.36	53.12
TYR	CA	453	62.60	103.71	54.28	: TYR	CB	453	64.09	64.09	54.35
TYR	CG	453	65.15	104.39	54.17	: TYR	CD1	453	65.58	65.58	55.28
TYR	CE1	453	66.52	106.10	55.07	: TYR	CD2	453	65.59	65.59	52.89
TYR	CE2	453	66.53	105.63	52.69	: TYR	CZ	453	66.97	66.97	53.78
TYR	OH	453	67.90	107.43	53.58	: TYR	C	453	62.23	62.23	55.47
TYR	O	453	61.99	105.78	55.33	: GLY	N	454	62.25	62.25	56.65
GLY	CA	454	61.83	104.77	57.78	: GLY	C	454	63.02	63.02	58.65
GLY	O	454	64.17	104.82	58.19	: THR	N	455	62.76	62.76	59.88
THR	CA	455	63.73	104.42	60.95	: THR	CB	455	63.31	63.31	61.56
THR	OG1	455	64.24	106.74	61.00	: THR	CG2	455	63.19	63.19	63.04
THR	C	455	63.60	103.14	61.82	: THR	O	455	62.63	62.63	61.71
GLY	N	456	64.59	102.92	62.69	: GLY	CA	456	64.59	64.59	63.66
GLY	C	456	65.99	101.75	64.27	: GLY	O	456	66.80	66.80	64.13
SER	N	457	66.23	100.68	65.04	: SER	CA	457	67.53	67.53	65.61
SER	CB	457	67.72	100.88	67.01	: SER	OG	457	68.74	68.74	67.74
SER	C	457	67.45	98.80	65.73	: SER	O	457	66.53	66.53	66.38
TRP	N	458	68.37	98.03	65.16	: TRP	CA	458	68.31	68.31	65.27
TRP	CB	458	68.13	96.02	63.83	: TRP	CG	458	66.88	66.88	63.10
TRP	CD2	458	66.75	97.75	62.42	: TRP	CE2	458	65.47	65.47	61.90
TRP	CE3	458	67.53	98.87	62.17	: TRP	CD1	458	65.75	65.75	63.01
TRP	NE1	458	64.92	96.48	62.27	: TRP	CZ2	458	64.94	64.94	61.13
TRP	CZ3	458	67.00	99.88	61.40	: TRP	CH2	458	65.72	65.72	60.87
TRP	C	458	69.54	96.00	65.98	: TRP	O	458	70.50	70.50	65.36
PRO	N	459	69.62	96.04	67.31	: PRO	CD	459	68.67	68.67	68.21
PRO	CA	459	70.73	95.52	68.08	: PRO	CB	459	70.63	70.63	69.39
PRO	CG	459	69.16	96.28	69.61	: PRO	C	459	70.71	70.71	68.25
PRO	O	459	69.71	93.32	67.92	: ASP	N	460	71.75	71.75	68.85
ASP	CA	460	71.82	92.02	69.07	: ASP	CB	460	73.08	73.08	69.89
ASP	CG	460	73.14	90.33	70.43	: ASP	OD1	460	73.37	73.37	69.64
ASP	OD2	460	72.94	90.17	71.64	: ASP	C	460	70.56	70.56	69.72
ASP	O	460	69.90	90.56	69.11	: GLY	N	461	70.19	70.19	70.92
GLY	CA	461	68.96	91.46	71.55	: GLY	C	461	69.10	69.10	72.80
GLY	O	461	68.15	90.52	73.57	: ALA	N	462	70.25	70.25	73.06
ALA	CA	462	70.33	89.14	74.18	: ALA	CB	462	71.58	71.58	74.12
ALA	C	462	70.31	89.83	75.52	: ALA	O	462	70.92	70.92	75.70
ASN	N	463	69.52	89.38	76.47	: ASN	CA	463	69.67	69.67	77.79

FIGURE 1 (cont.)

ASN CB	463	68.38	89.74	78.58	ASN CG	463	68.51	68.51	80.00
ASN OD1	463	69.45	89.94	80.74	ASN ND2	463	67.56	67.56	80.49
ASN D21	463	66.78	91.24	79.94	ASN D22	463	67.71	67.71	81.41
ASN C	463	70.79	89.09	78.38	ASN O	463	70.65	70.65	78.57
ILE N	464	71.89	89.77	78.68	ILE CA	464	73.10	73.10	79.20
ILE CB	464	74.16	90.31	79.28	ILE CG2	464	74.59	74.59	80.71
ILE CG1	464	75.35	89.90	78.39	ILE CD1	464	76.36	76.36	78.97
ILE C	464	72.89	88.38	80.50	ILE O	464	73.71	73.71	80.84
ASN N	465	71.82	88.63	81.24	ASN CA	465	71.57	71.57	82.45
ASN CB	465	70.80	88.75	83.43	ASN CG	465	71.55	71.55	83.83
ASN OD1	465	71.19	91.11	83.40	ASN ND2	465	72.60	72.60	84.64
ASN D21	465	72.86	89.06	85.00	ASN D22	465	73.07	73.07	84.83
ASN C	465	70.78	86.63	82.19	ASN O	465	70.44	70.44	83.11
PHE N	466	70.40	86.33	80.95	PHE CA	466	69.73	69.73	80.66
PHE CB	466	68.62	85.30	79.63	PHE CG	466	67.46	67.46	80.09
PHE CD1	466	67.30	86.50	81.43	PHE CD2	466	66.58	66.58	79.15
PHE CE1	466	66.26	87.30	81.81	PHE CE2	466	65.53	65.53	79.54
PHE CZ	466	65.38	87.78	80.87	PHE C	466	70.72	70.72	80.10
PHE O	466	70.39	82.92	79.88	MET N	467	71.92	71.92	79.71
MET CA	467	72.90	83.73	79.04	MET CB	467	73.99	73.99	78.45
MET CG	467	73.48	85.57	77.45	MET SD	467	72.52	72.52	76.08
MET CE	467	73.77	83.94	75.26	MET C	467	73.55	73.55	79.98
MET O	467	73.59	82.94	81.19	PRO N	468	74.01	74.01	79.48
PRO CD	468	73.49	80.90	78.31	PRO CA	468	74.96	74.96	80.22
PRO CB	468	75.06	79.54	79.39	PRO CG	468	74.66	74.66	77.99
PRO C	468	76.27	81.57	80.39	PRO O	468	76.64	76.64	79.58
ILE N	469	76.90	81.03	81.43	ILE CA	469	78.20	78.20	82.01
ILE CB	469	79.31	81.72	80.98	ILE CG2	469	80.61	80.61	81.69
ILE CG1	469	79.46	80.82	79.75	ILE CD1	469	79.38	79.38	79.83
ILE C	469	78.05	82.42	83.03	ILE OT1	469	77.51	77.51	82.71
ILE OT2	469	78.42	82.16	84.16	NAG C1	86A	80.32	80.32	31.26
NAG C2	86A	80.66	91.34	29.83	NAG N2	86A	81.23	81.23	29.81
NAG C7	86A	82.54	92.89	29.87	NAG O7	86A	83.35	83.35	29.96
NAG C8	86A	82.98	94.35	29.82	NAG C3	86A	79.45	79.45	28.93
NAG O3	86A	79.90	91.59	27.60	NAG C4	86A	78.69	78.69	29.11
NAG O4	86A	77.51	90.10	28.30	NAG C5	86A	78.29	78.29	30.56
NAG O5	86A	79.50	89.81	31.32	NAG C6	86A	77.43	77.43	30.77
NAG O6	86A	77.90	87.56	30.01	NAG C1	146A	86.70	86.70	83.15
NAG C2	146A	86.32	79.61	84.41	NAG N2	146A	84.99	84.99	84.57
NAG C7	146A	83.86	79.69	84.35	NAG O7	146A	83.89	83.89	83.93
NAG C8	146A	82.53	79.00	84.60	NAG C3	146A	86.67	86.67	85.59
NAG O3	146A	86.20	80.01	86.83	NAG C4	146A	88.16	88.16	85.62
NAG O4	146A	88.54	81.49	86.72	NAG C5	146A	88.69	88.69	84.32
NAG O5	146A	88.12	80.60	83.18	NAG C6	146A	90.22	90.22	84.15
NAG O6	146A	90.66	79.77	84.27	NAG C1	200A	108.62	108.62	59.44
NAG C2	200A	109.75	77.56	60.28	NAG N2	200A	110.43	110.43	61.09
NAG C7	200A	110.11	78.83	62.38	NAG O7	200A	109.18	109.18	62.93
NAG C8	200A	110.87	79.90	63.17	NAG C3	200A	110.76	110.76	59.36
NAG O3	200A	111.71	76.31	60.21	NAG C4	200A	110.05	110.05	58.50
NAG O4	200A	110.95	75.17	57.51	NAG C5	200A	108.87	108.87	57.75
NAG O5	200A	108.02	77.06	58.69	NAG C6	200A	108.04	108.04	57.00
NAG O6	200A	107.53	74.40	57.94	NAG C1	200B	111.16	111.16	57.67
NAG C2	200B	111.86	73.13	56.51	NAG N2	200B	111.04	111.04	55.31
NAG C7	200B	111.21	73.92	54.27	NAG O7	200B	111.95	111.95	54.34
NAG C8	200B	110.40	73.68	53.00	NAG C3	200B	112.20	112.20	56.78
NAG O3	200B	112.94	71.11	55.74	NAG C4	200B	112.95	112.95	58.10
NAG O4	200B	113.10	70.17	58.29	NAG C5	200B	112.12	112.12	59.22
NAG O5	200B	111.91	73.53	58.89	NAG C6	200B	112.69	112.69	60.66

FIGURE 1 (cont.)

H2O OH2 182	82.72	101.43	58.30	: H2O OH2 183	87.58	87.58	57.43
H2O OH2 184	96.22	102.15	37.47	: H2O OH2 185	94.73	94.73	40.55
H2O OH2 187	78.28	117.08	59.75	: H2O OH2 189	82.63	82.63	62.08
H2O OH2 190	83.42	101.41	61.07	: H2O OH2 191	87.87	87.87	68.82
H2O OH2 192	84.85	98.37	72.05	: H2O OH2 194	85.07	85.07	62.47
H2O OH2 195	89.81	111.68	64.39	: H2O OH2 197	78.79	78.79	61.44
H2O OH2 198	88.42	110.10	56.24	: H2O OH2 201	94.26	94.26	50.76
H2O OH2 204	94.76	113.64	56.53	: H2O OH2 205	83.93	83.93	57.60
H2O OH2 206	83.95	108.68	41.55	: H2O OH2 207	81.33	81.33	70.75
H2O OH2 209	72.45	106.06	55.31	: H2O OH2 210	68.10	68.10	55.92
H2O OH2 211	73.97	95.00	70.32	: H2O OH2 212	74.40	74.40	73.04
H2O OH2 215	65.93	94.45	71.39	: H2O OH2 216	71.63	71.63	65.29
H2O OH2 217	69.94	100.28	45.21	: H2O OH2 221	85.83	85.83	71.32
H2O OH2 224	68.00	106.89	62.11	: H2O OH2 225	66.97	66.97	64.62
H2O OH2 226	67.37	107.99	59.65	: H2O OH2 227	76.93	76.93	69.73
H2O OH2 228	77.12	82.17	66.21	: H2O OH2 229	77.08	77.08	63.43
H2O OH2 230	75.89	74.57	73.14	: H2O OH2 233	70.51	70.51	69.80
H2O OH2 234	75.33	88.62	42.44	: H2O OH2 236	76.59	76.59	40.24
CA XA CA	93.46	103.91	63.53	:			

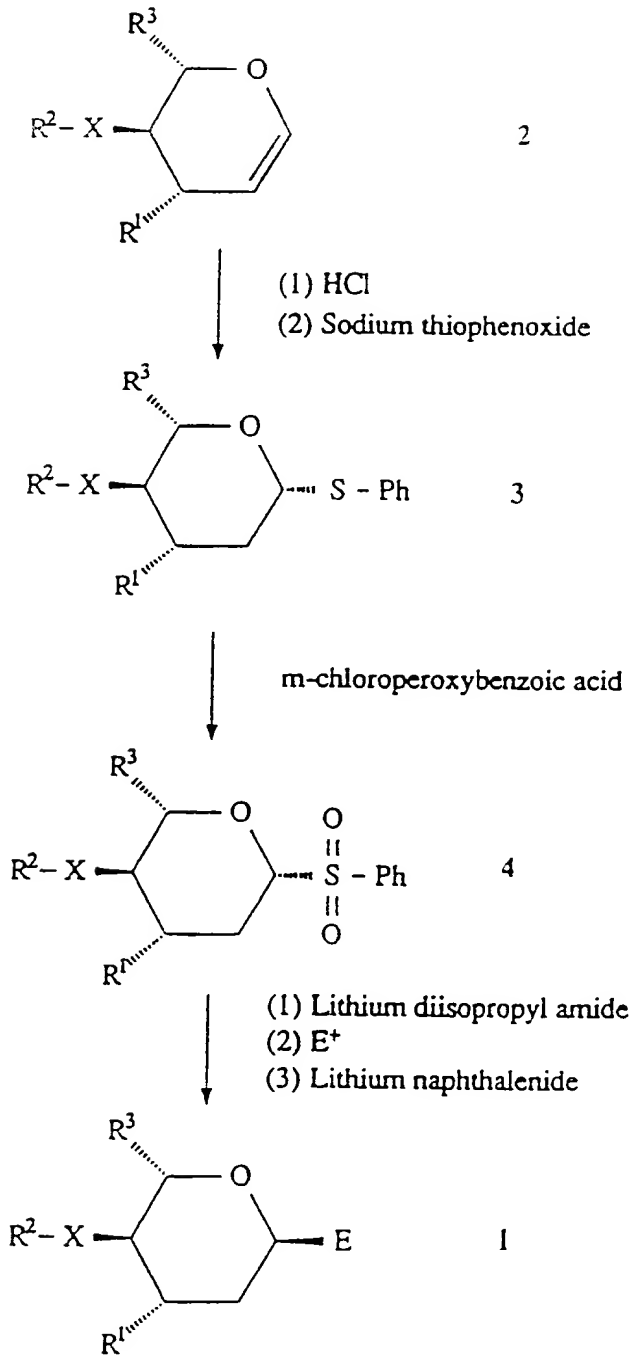
SIA	C1	SIAL	90.06	93.33	66.69	: SIA	O1A	SIAL	89.98	89.98	66.22
SIA	O1B	SIAL	89.34	92.99	67.63	: SIA	C2	SIAL	91.05	91.05	66.09
SIA	O2	SIAL	91.97	91.94	67.10	: SIA	C3	SIAL	90.23	90.23	65.63
SIA	C4	SIAL	90.97	90.20	64.61	: SIA	O4	SIAL	90.80	90.80	64.86
SIA	C5	SIAL	92.47	90.55	64.64	: SIA	N5	SIAL	93.17	93.17	63.65
SIA	C10	SIAL	94.07	88.77	63.9?	: SIA	O10	SIAL	94.43	94.43	65.07
SIA	C11	SIAL	94.62	88.08	62.6	: SIA	111	SIAL	94.28	94.28	61.77
SIA	112	SIAL	94.31	87.03	62.6	: SIA	113	SIAL	95.70	95.70	62.71
SIA	C6	SIAL	92.68	92.06	64.25	: SIA	O6	SIAL	91.78	91.78	64.99
SIA	C7	SIAL	94.11	92.50	64.57	: SIA	O7	SIAL	94.38	94.38	65.93
SIA	C8	SIAL	94.35	93.97	64.21	: SIA	O8	SIAL	94.10	94.10	62.82
SIA	C9	SIAL	95.83	94.35	64.50	: SIA	O9	SIAL	96.59	96.59	63.33

FIGURE 3

3-Fluoro-1,1,1,3,5,5,5-heptanitropentane

PEN F1	5	95.14	90.03	63.25	:	PEN C2	5	94.67	94.67	63.89
PEN C3	5	94.26	91.59	64.87	:	PEN C4	5	94.46	94.46	64.42
PEN C5	5	93.14	89.33	64.38	:	PEN C6	5	93.11	93.11	63.60
PEN N7	5	91.68	87.43	63.72	:	PEN N8	5	94.06	94.06	64.09
PEN N9	5	93.35	88.24	62.12	:	PEN N10	5	95.42	95.42	65.50
PEN N11	5	94.59	94.05	64.55	:	PEN N12	5	96.14	96.14	63.42
PEN N13	5	93.76	92.76	62.65	:	PEN O14	5	91.16	91.16	64.80
PEN O15	5	91.25	86.88	62.74	:	PEN O16	5	93.61	93.61	64.27
PEN O17	5	95.23	87.27	64.19	:	PEN O18	5	92.68	92.68	61.60
PEN O19	5	94.19	87.51	61.57	:	PEN O20	5	96.61	96.61	65.25
PEN O21	5	94.90	89.16	66.51	:	PEN O22	5	93.10	93.10	64.81
PEN O23	5	95.43	94.85	64.23	:	PEN O24	5	96.38	96.38	62.25
PEN O25	5	96.92	92.28	64.35	:	PEN O26	5	93.83	93.83	62.04
PEN O27	5	93.09	91.82	62.41	:					

Figure 4



Ph = phenyl ; E = CO_2H (1a), $PO(OH)_2$ (1b) or SO_2H (1c).

Figure 5

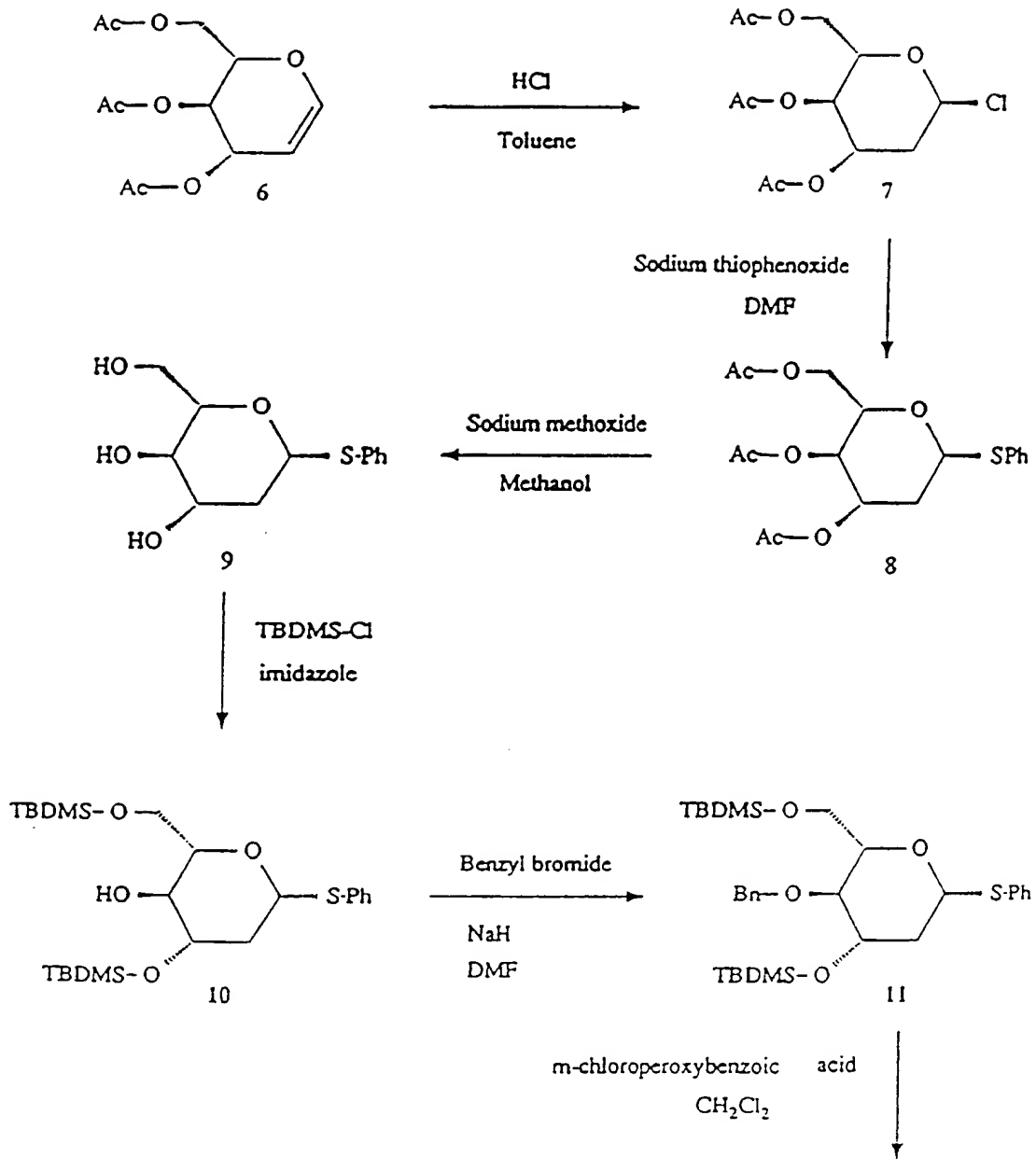

Ac—O
Ac—O
Ac—O
O
6
HCl
Toluene
Ac—O
Ac—O
Ac—O
Cl
7
Sodium thiophenoxide
DMF
HO
HO
HO
S-Ph
9
Sodium methoxide
Methanol
Ac—O
Ac—O
Ac—O
SPh
8
TBDMS-Cl
imidazole
TBDMS—O
HO
TBDMS—O
S-Ph
10
Benzyl bromide
NaH
DMF
TBDMS—O
Bn—O
TBDMS—O
S-Ph
11
m-chloroperoxybenzoic acid
CH_2Cl_2

Figure 5 (cont.)

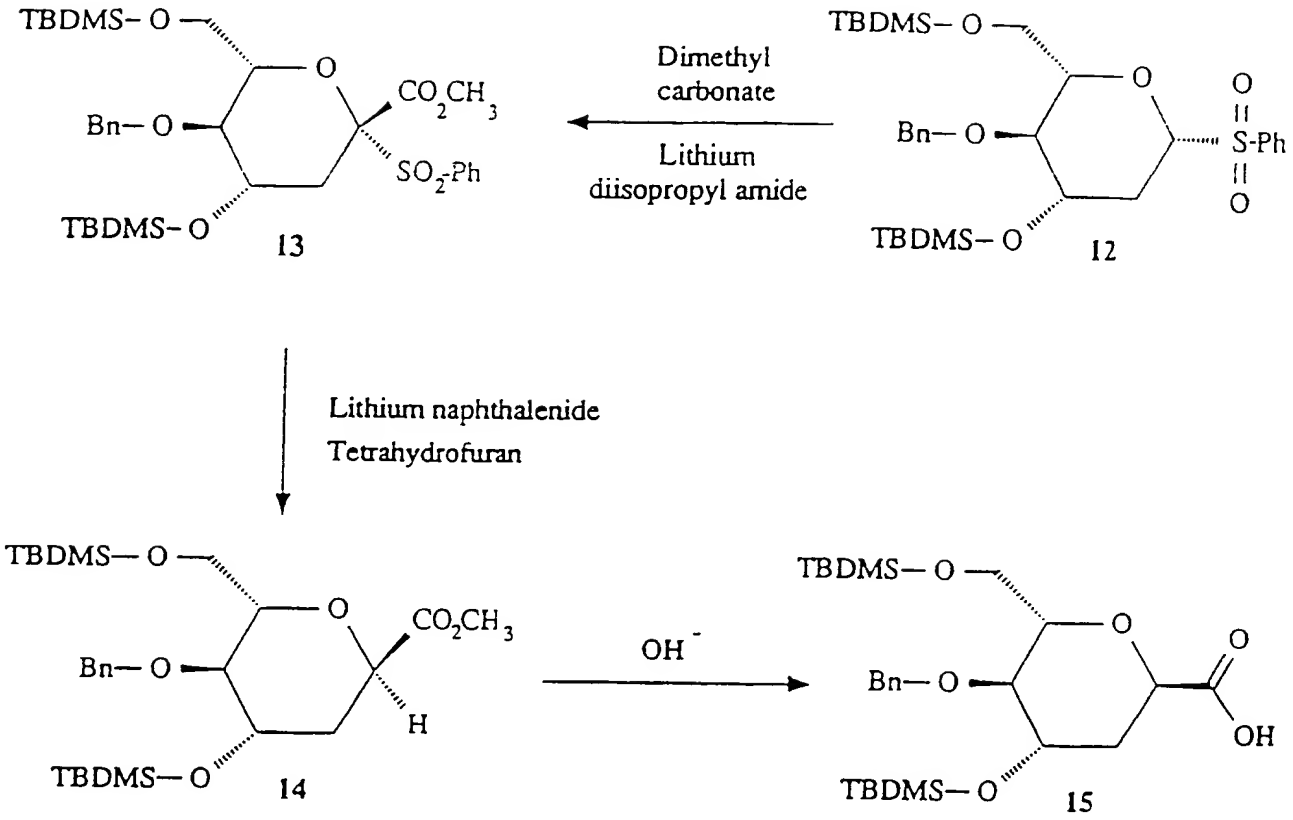


Figure 6

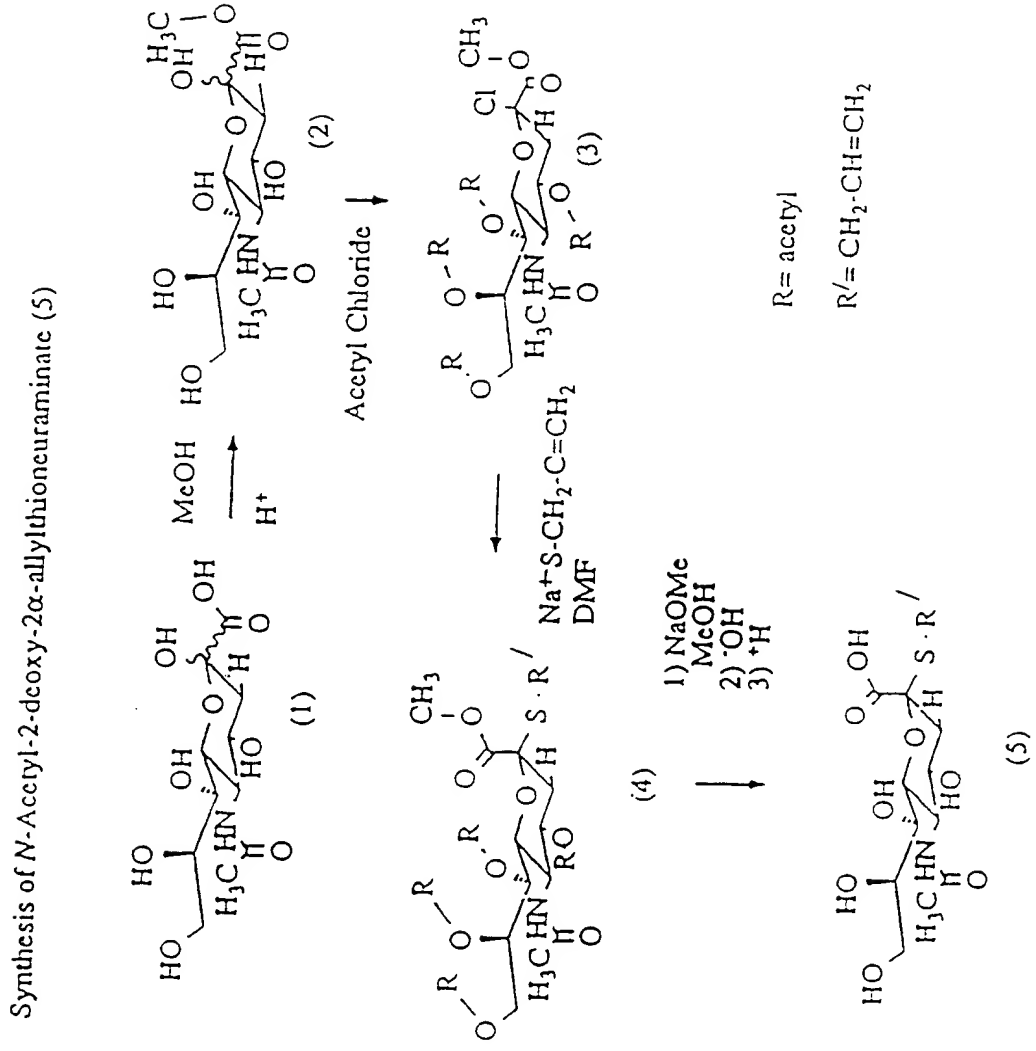
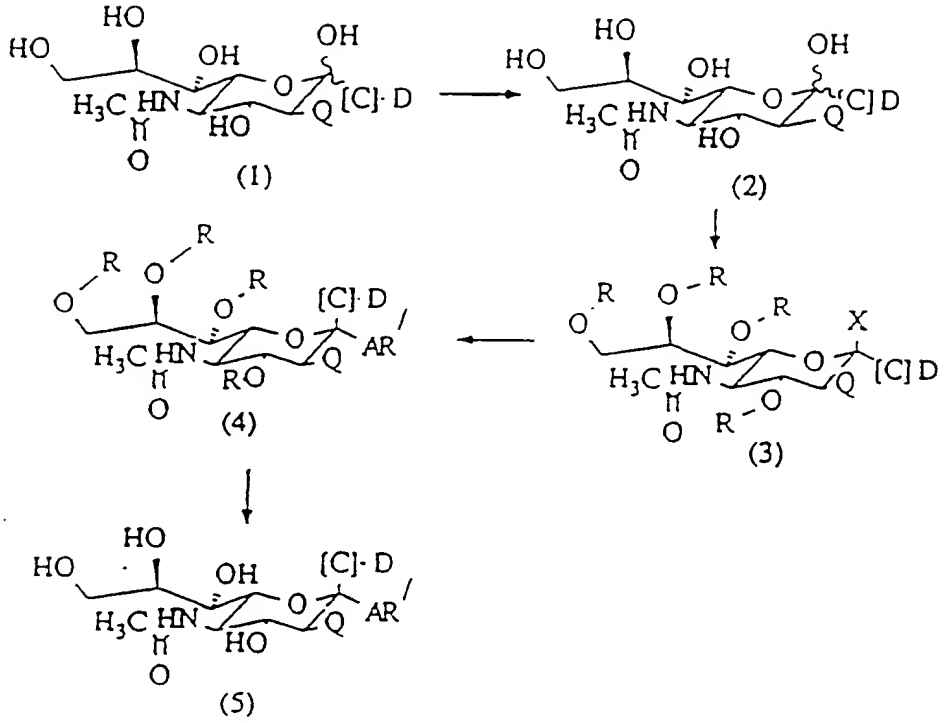

Synthesis of N-Acetyl-2-deoxy-2α-allylthioneuraminate (5)
MeOH
H+
Acetyl Chloride
Na+S-CH2-C=CH2
DMF
1) NaOMe
MeOH
2) OH
3) H
R= acetyl
R/= CH2-CH=CH2
(1)
(2)
(3)
(4)
(5)

Figure 7

General Reaction Scheme



Q= see R^2 in text
X= halogen e.g. Cl, Br , see R in general formula I
R= R^4 in text
[C]-D= electron-withdrawing group, see E in text
AR'= R^1 in text, general formula II

INTERNATIONAL SEARCH REPORT

International Application No. PCT/AU 90/00501

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 6

According to International Patent Classification (IPC) or to both National Classification and IPC

Int. Cl.[5] A61K 31/70, 45/00, C07H 5/06, C07D 309/28, 309/30, 309/22, 309/20

II. FIELDS SEARCHED

Minimum Documentation Searched 7

Classification System	Classification Symbols
IPC	C07H 5/06, C07D 309/20, 309/22, 309/28, 309/30; A61K 31/70: Keywords NEURAMIN: or SIAL: DERWENT DATABASES: WPI, WPIL, USPA: Keywords INFLUENZA VIRUS NEURAMIN:

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched 8

AU : IPC as above
CHEM ABS using Keywords above

III. DOCUMENTS CONSIDERED TO BE RELEVANT 9

Category*	Citation of Document, 11 with indication, where appropriate, of the relevant passages 12	Relevant to Claim No 13
X	Virology, Volume 58, issued 1974, P. Meindl et al, "Inhibition of Neuraminidase Activity by Derivatives of 2-deoxy-2,3-dehydro-N-acetyl neuraminic acid", pages 457-463	(1,7-15)
X	Virology, Volume 59, issued 1974, P. Palese et al, "Inhibition of Influenza and Parainfluenza Virus Replication in Tissue Culture by 2-deoxy-2,3-dehydro-N-trifluoroacetylneuraminic acid (FANA)", pages 490-498	(1,7-15)
X	Biochemical and Biophysical Research Communications, Volume 83, Number 4, issued 1978, C.A. Miller et al, "Mechanism of Arthrobacter Sialophilus Neuraminidase: The Binding of Substrates and Transition-state Analogs", pages 1479-1487	(1,7-15)

(continued)

* Special categories of cited documents: 10

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
24 January 1991 (24.01.91)	16 February 1991
International Searching Authority	Signature of Authorized Officer
Australian Patent Office	JOHN G. HANSON

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X	Tetrahedron Letters, Volume 29, Number 30, issued 1988, W. Schmid et al, "Synthesis of both Epimeric 2-deoxy-N-acetylneuraminic acids and their Behaviour towards CMP-Sialate Synthetase-A Comparison with 2-β-methylketoside of N-acetylneuraminic acid", pages 3643-3646	(1,14-21)
X	Carbohydrate Research, Volume 127, issued 1984, M.N. Sharma and R. Eby, "Synthesis and Conformational Studies of 2-β-chloro, 2-α-fluoro and 2-β-fluoro Derivatives of 2-deoxy-N-acetyl-neuraminic acid", pages 201-210	(1,17-21)
X,P	AU,A, 34798/89 (MECT CORPORATION) 16 November 1989 (16.11.89), see claims, page 4 lines 15-26	(1,18-21)
X,P	US,A, 4914195 (H. OGURA et al) 3 April 1990 (03.04.90), see claims	(37)

V. [ ] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.[ ] Claim numbers ..., because they relate to subject matter not required to be searched by this Authority, namely:

2.[ ] Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3.[ ] Claim numbers ..., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4 (a):

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

This International Searching Authority found multiple inventions in this international application as follows:

1.[ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2.[ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3.[ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON
INTERNATIONAL APPLICATION NO. PCT/AU 90/00501

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report	Patent Family Members		
US 4914195	DE 3219209	FR 2506313	GB 2101588
	HK 275/89	JP 58000992	SG 112/88
	US 4447600		
AU 34798/89	DK 2329/89	EP 341735	IL 90271
	JP 1287029		

END OF ANNEX